Detection and assessment of motor disorders in Parkinson's disease

een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

Proefschrift

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Introduction

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General Introduction

Parkinson's disease (PD) is characterized by many symptoms, including bradykinesia (slowness of voluntary movements), hypokinesia (lack of voluntary movements), akinesia (difficulty to start a movement), tremor (spontaneous rhythmic repetitive alternating movements, typically at a frequency of 4 to 6 Hz), rigidity (increased resistance to passive manipulation of joints) and postural disturbances (stooped posture, falls, and difficulty in organizing the trunk and limbs, such as rolling in bed and getting out of chairs or automobiles). The cause of PD is still unknown, but the symptoms are a consequence of a reduction of dopamine in the Substantia Nigra. Dopaminergic drugs, like levodopa and dopamine agonists, are highly effective in the treatment of PD. Initially, levodopa taken three or four times a day reduces the symptoms and signs of the disease throughout the day and the patient might return to full normal function. However, with each year of levodopa treatment, the number of PD patients who suffer from fluctuations in the motor response increases. Many of these patients start to fluctuate between the "off" state (re-emergence of PD symptoms because the effect of Levodopa wears off a few hours after levodopa intake) and the "on" state, in which levodopa is active and improves the patients' motor performance. In addition to these fluctuations, patients can suffer from abnormal involuntary movements in the "on" state. The presence of these abnormal involuntary movements is a side effect of levodopa therapy and is therefore commonly referred to as levodopa induced dyskinesia (LID). The actual emergence of dyskinesias throughout the day depends mainly on the timing and quantity of each individual levodopa dose and also depends on stress, food and many other factors, be it to a lesser extent (Horstink et al., 1990a,b; Nutt, 1990; Lang and Lozano, 1998a,b). For patients, who fluctuate and who suffer from LID, it becomes more difficult to manage the disease. In these cases, adjustment of the timing and dose of Levodopa intake will eliminate the symptoms of dyskinesia. However, determining the proper timing and dose requires continuous assessment of the motor state of these patients in relation to the dosing schedule in daily life.

Because continuous supervision by a physician to determine the symptoms of dyskinesia is impossible for practical purposes, patients have to keep a diary in which they register their observed fluctuations in motor state during the day. Usually, patients register in their diary whether they are in an "on" state, have LID, or are in an "off" state (re-emergence of PD symptoms) every half hour or hourly. Because the patient's motor function depends on more factors than time and dose of levodopa alone, the patients' motor state can differ from day to day. Therefore, diaries have to be kept for at least three or four days in order to obtain sufficient insight in the average diurnal pattern. However, this self-report of the motor state has its limitations and is frequently unreliable (Golbe and Pae, 1988; Brown et al., 1989; Goetz et al., 1997; Vitale et al., 2001). For example, patients may have no insight in their symptoms and may not be able to discriminate between LID and PD features. They may also

forget to register each half hour or may be too disabled to write. At last, many patients feel the method is rather cumbersome and they do not take the effort to update the diary every half hour. Another negative effect of this method is the fact that patients have to focus on their motor functioning all day long, whereas distraction is a much better way of life. Assessment of the behavior by an expert would be a solution. However, motor behavior in a hospital environment does not always mimic behavior at home, and long-term observations are time-consuming. For these reasons, an automatic ambulatory device that can register and classify the motor state of a PD patient with fluctuations would be highly useful (Brown and Manson, 1999).

For a successful assessment of the motor state of PD patients, Parkinsonian symptoms and involuntary movements, like LID, have to be detected and distinguished from normal, voluntary activities. The main characteristics of parkinsonian symptoms are a lack of activity (hypokinesia) and slowness of movement (bradykinesia). Hypokinesia and to a lesser extent bradykinesia can be detected by assessing the amount and intensity of movements. However, hypokinetic periods will be hard to distinguish from voluntary inactivity. An advantage of assessing dyskinesia is that dyskinesia and fluctuations in motor response frequently coexist. This means that by a proper assessment of dyskinesia, physicians can roughly indicate the occurrence of fluctuations in motor response as far as they coexist with dyskinesia. Furthermore, pharmacological and surgical interventions to reduce these dyskinesias are of increasing interest (Lozano et al., 1995; Brotchie, 1998; Verhagen et al., 1998; Pollak, 1999; Manson et al., 2000b; Fraix et al., 2000; Lang, 2000; Rascol, 2000b). For these reasons, this thesis primarily focuses on the assessment and detection of LID. A proper detection of LID means that fluctuations in motor response can reasonably be assessed and that new interventions to reduce LID can objectively be evaluated. Therefore, the major purpose of this thesis is the development of a method for automatic assessment and detection of dyskinesia in daily life of a patient.

Although this thesis, like many other studies, mainly focused on motor disorders in PD, there is increasing evidence that the main cause of the motor disorders in PD might not be found in the motor system itself, but rather in the processing of sensory input to the motor system. Several studies (Schneider et al., 1987, Filion et al., 1988; Klockgether et al., 1995, Rickards and Cody, 1997; Jobst et al., 1997, Zia et al., 1999, Boecker et al., 1999; Lewis and Byblow, 2002) have reported that PD patients do not, or do not adequately use sensory information in simple motor tasks. In order to explore this in more detail, we have investigated the role of visual and proprioceptive information in pointing movements to remembered visual targets in PD.

This introduction starts with a description of the phenomenology and pathophysiology of levodopa induced dyskinesias. Subsequently, the methods for acquisition of human movements in daily life will be discussed. The third section of the introduction will explain the

analysis of the accelerometer signal and the role of neural networks in the assessment of dyskinesia. In the final section of the introduction, an outline of the thesis will be given.

Levodopa Induced dyskinesia

PD results from the degeneration of cells in the Substantia Nigra, which is part of the Basal Ganglia, also called the extrapyramidal system. These nigral cells produce dopamine, which exerts its effects in the striatum, especially in the putamen. The Dopaminergic nigrostriatal projection plays a major role in motor control. The reduction of striatal dopamine in the Basal Ganglia is a major neurochemical deficit in PD. The clinical manifestation of PD generally begins when patients have lost about 60 to 80% of their dopamine producing cells. One of the basal ganglia functions is that it plays a role in directing and controlling movements. As a result of the reduction of dopamine in the striatum in PD, patients are unable to direct and control their movements in a normal manner. The reduction of dopamine in the striatum can be remedied by artificial administration of dopamine. Studies have shown that dopaminergic drugs, like levodopa and dopamine agonists, are highly effective in the treatment of PD. However, dopamine does not cross the blood-brain barrier in appreciable amounts, which makes dopamine not effective as a drug for oral administration. Levodopa, the precursor of dopamine, easily gains access to the brain and it has been shown that levodopa administration increases striatal dopamine levels in human brains with PD (Cotzias, 1967; Marsden, 1994). This explains why levodopa is the regular drug to reduce Parkinson symptoms.

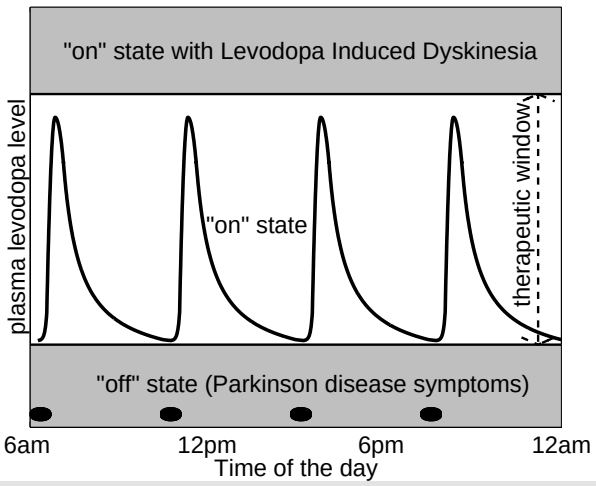

Figure 1.1. Schematic view of the plasma levodopa level in patients with Parkinson's disease. Patients in the early stage of the disease enjoy a long-term response to levodopa taken four times a day. These patients stay easily in the "on" state in which levodopa is active and improves the patients' motor performance (therapeutic window).

Patients with early Parkinson's disease enjoy a long-term response to each levodopa dose. Initially, levodopa taken three to four times a day reduces the parkinsonian symptoms during the whole day (see Figure 1.1). Unfortunately, the combination of disease progression

and chronic levodopa therapy results in a less clear response after 3 to 5 years. Over the years, the antiparkinson effect of each individual levodopa dose lasts shorter resulting in the emergence of end-of-dose effect, also termed wearing-off effect, necessitating levodopa intake more frequently. In an even more severe stage of PD, when the therapeutic window has become very narrow, the individual dose leads to an abrupt switching response, which is referred to as “on-off” phenomenon. The “on” state refers to the state in which levodopa is active and does improve the patients’ motor performance. The “off” state refers to the state in which patients suffer from PD symptoms because the effect of levodopa wears off. In addition to the wearing-off effect and motor fluctuations, patients also develop involuntary movements called dyskinesias. When these dyskinesias first appear, they are usually associated with high levodopa levels and may be prevented and minimized by lowering levodopa intake (see Figure 1.2). Later on, however, the therapeutic window of levodopa narrows and dyskinesia occurs at plasma levodopa levels equal to or lower than those needed to induce an antiparkinson effect (see Figure 1.2).

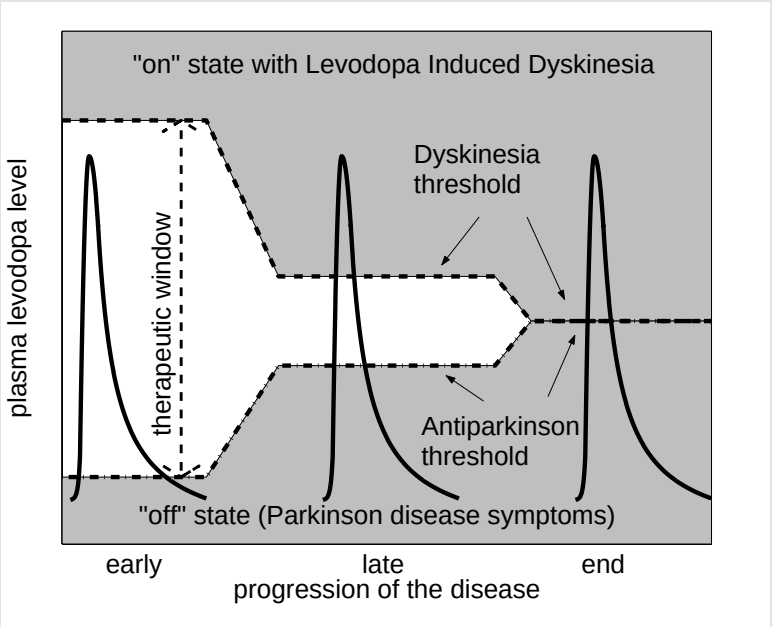

Figure 1.2. Schematic view of narrowing the therapeutic window with progression from early to end-stage PD.

Involuntary movements are a common problem, occurring in 30% to 80% of PD patients treated chronically with levodopa (Marsden et al., 1981; Nutt et al., 1990; Quinn, 1995; Obeso et al., 1997; Rascol, 2000a). Dyskinesia commonly occurs in the face, neck or limbs but may occur in any skeletal muscle group. Furthermore, dyskinesia is usually more prominent in more severely affected patients and is worse on the side most affected by the parkinsonism (Mones et al., 1971; Marconi et al., 1994; Horstink et al., 1990a). Dyskinesia generally appears in parkinsonian patients with an initially good therapeutic response to levodopa. It is commonly believed that the onset of dyskinesia is the consequence of a

combination of pathology in the substantia nigra and levodopa treatment (Mena et al., 1970; Chase et al., 1973; Boyce et al., 1990; Nutt, 1990; Horstink et al., 1990b; Bedard et al., 1992; Nutt and Holford, 1996; Mouradian et al., 1989). Levodopa treatment of normal subjects, and of subjects with other movement disorders, or other neurological disorders generally does not produce dyskinesia (Mena et al., 1970; Cotzias et al., 1967; Chase et al., 1973; Obeso et al., 1989; Arts et al., 1991; Rajput et al., 1997). Therefore, it is suggested that the more severe the pathology in the substantia nigra, the more rapidly involuntary movements appear and the lower the dose of levodopa at which these involuntary movements occur. Dyskinesias in PD are schematically classified into three categories: peak dose dyskinesia, diphasic dyskinesias, and off period dyskinesia. Peak dose dyskinesia is the most common pattern of LID and occurs when levodopa effects on parkinsonian symptoms are maximal (Horstink et al., 1990a; Nutt, 1990; Chase, 1993;Marsden, 1994; Quinn, 1998; Fahn, 2000). Diphasic dyskinesia appears when the plasma level of levodopa is rising or falling but not during the peak. These patients suffer from dyskinesias at the beginning and end of the clinically beneficial period of levodopa (Nutt, 1990; Marsden, 1994; Quinn, 1998; Fahn, 2000). Off-period dyskinesia tends to be dystonic and occurs in the mornings when a patient has been without levodopa overnight as well as during “off” periods during the day.

There are at present many open questions as to exactly what changes in the motor response to levodopa during long-term levodopa therapy, and how it relates to the patients’ perception of motor fluctuations. Much research has been done to identify which factors predict the levodopa response, the fluctuations in motor response, and the occurrence of LID (Tolosa et al., 1975; Fabrini et al., 1988; Mouradian, 1988; Nutt, 1990; Horstink et al., 1990a,b; Nutt et al., 1997a,b; Jenner, 2000a,b; Nutt et al., 2002). The response duration of levodopa appeared to be best predicted by the severity of the patient’s disease (Fabrini et al., 1988; Horstink et al. 1990b). The occurrence of fluctuations appeared to be significantly correlated with the duration of PD and with the duration of levodopa therapy (Cotzias et al., 1967; Mones et al., 1971; Nutt, 1990; Horstink et al., 1990b).

Measurement of movements

Quantitative assessment of human motor control has greatly contributed to the present understanding of the basic principles, which underlie human motor behavior and motor disorders. The most commonly used and most accurate technique to monitor and study human motor behavior is by using optical motion analysis systems. The main disadvantages of optical motion analysis systems are that they are expensive and that they can only measure movements in a restricted space. Due to these limitations, they can only be used in a laboratory setting. However, sophisticated equipment alone is not a guarantee for success in the detection of motor disorders. In many situations, motor disorders may occur only in very specific situations, which are hard to imitate in a laboratory setting. A good

example is stumbling in elderly people. They do not have a specific motor disorder but tend to fall more easily than normal subjects in complex situations because of the limited information-processing capability of elderly people (Tang and Woollacott 1998; Schillings et al., 2001; Najafi et al., 2002). Managing the motor state and thus the occurrence of LID by PD patients is another example of a motor disorder that occurs in daily life at variable periods of the day. Therefore, testing a subject for an hour in a laboratory will not provide the information that is necessary to determine the severity of LID and the time of occurrence of LID.

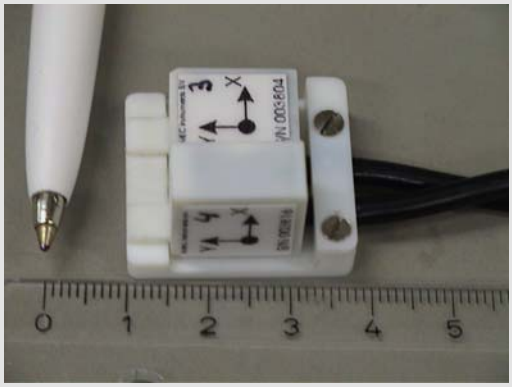

Figure 1.3. Two biaxial accelerometers resulting in a set of 3 orthogonal accelerometers which have been used in the studies of chapter 3, 4, and 5 in this thesis.

Recently, body-mounted sensors like accelerometers, gyroscopes, electrogoniometers, and earth-magnetic field sensors have been used to obtain data about kinematic parameters, mainly in a laboratory setting (Willemsen et al., 1990; Wagenaar and Emmerik, 2000; Mayagoitia et al., 2002, Miyazaki, 1997; Kemp et al., 1998; Bussmann et al., 1998a,b; van Someren et al., 1998; Tong and Granat, 1999; Tulen et al., 2001). Due to new developments in microelectronics, these sensors have become smaller, cheaper, more robust, and more accurate than before. Figure 1.3 shows two biaxial accelerometers, which were used in this thesis. Accelerometers are most frequently used for the analysis of gait. One of the most important advantages of body-mounted sensors is that they can be used in daily life. Several investigators have studied the possibilities of accelerometry to detect postures and movement in daily life (Veltink et al., 1996; Bussman et al., 1998a,b; Kiani et al., 1998; Dunnewold et al., 1998; Fahrenberg et al., 1997). These so-called activity monitors were designed to detect various daily life activities. Bussman et al. (1998a,b) used 4 body fixed accelerometers and were able to assess static activities (standing, sitting, and lying) and dynamic activities (walking, transitions, cycling, and climbing stairs). Activity monitors have also been used to identify the energy expenditure in daily life (Montoye et al., 1983; Bouten et al., 1994; Tuomisto et al., 1996; Eston et al., 1998). In PD patients, accelerometry based movement sensors have been used to measure the amount and intensity of movements of various body segments and to detect tremor. (Someren et al., 1993; Timmer

et al., 1996; Someren et al., 1998; Tulen et al., 2001; Rajaraman et al., 2000; Letz and Gerr, 2000; Hoff et al., 2001b). Studies that developed tremor detection algorithms for long-term assessment used a combination of Fourier analysis and characteristics of the accelerometer signal to detect tremor. These studies found a false positive error of about 5% for their tremor detection algorithm and were successful in discriminating tremor from other movements (Someren et al., 1998; Hoff et al., 2001b). Studies evaluating hypokinesia and bradykinesia in long-term recordings mostly used a wrist-worn activity monitor. These wrist-worn activity monitors appeared to be a reliable method to determine hypokinetic periods during a day (Van Hilten et al., 1993a,b, 1995; Dunnewold et al., 1997, 1998; Katayama, 2001). However, the main problem of these wrist-worn activity monitors is that they measure movements of the wrist only, without any knowledge of movements of other limbs. So far, only Dunnewold et al. (1998) reported results of accelerometers placed on four segments of the body in PD patients. They were able to reliably identify body postures such as sitting, lying, and standing. In addition, they found that PD patients showed significantly smaller bradykinesia (defined as the mean value of the vectorial sum of the accelerometer signals for each pair of sensors on a segment) and larger hypokinesia values (defined as mean duration of immobility periods) than controls. However, these authors did not investigate whether combining body positions with periods of immobility resulted in an increase in the performance of assessing hypokinesia and bradykinesia. In conclusion, accelerometry appears to be helpful in assessment of motor disorders of PD in daily life.

Dyskinesia is characterized by the occurrence of abnormal involuntary movements. This triggered several researchers to use accelerometry or other body mounted sensors to assess dyskinesia in a more quantitative way. Burkhard et al. (1999) used a rotation-sensitive movement monitor (RoMM) and could successfully quantify and characterize dyskinesia for patients who were asked to abstain from voluntary movements. In a study by Hoff et al. (2001a) patients were tested in a set of seven tasks of one minute duration each. These authors used a linear discriminant analysis and could assess the severity of LID for tasks in which patients abstained from voluntary movements. However, they had problems in assessing LID when voluntary movements were present, like in drinking and walking. In another study, Manson et al. (2000a) attached a triaxial accelerometer to the shoulder and showed that the accelerations in the 1-3 Hz frequency band correlated well with the AIMS scale (Guy, 1976) for various tasks. They were able to assess the severity of LID, even when patients made voluntary movements. However, a main limitation in the study by Manson et al. (2000a) may be the low specificity for mild dyskinesias. Because all patients in that study suffered from severe dyskinesia during the test, the method was not validated to assess mild dyskinesias, which is important to assess LID in daily life and to evaluate medication and surgical treatment to reduce LID. This overview of studies for the assessment of LID illustrates that a successful method is not yet available but that accelerometers may provide

the opportunity to assess dyskinesias in daily life settings when advanced algorithms are available to distinguish dyskinesia from voluntary movements.

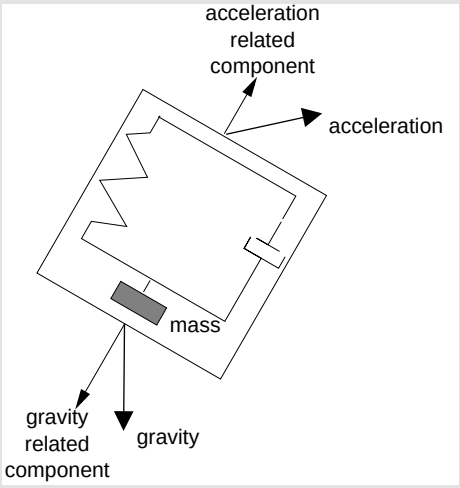

Figure 1.4. A single axis accelerometer consists of a mass, connected to a frame by beams, which can be represented by a damped spring. The accelerometer measures a contribution of gravity related to the orientation of the accelerometer and a contribution related to linear acceleration of the accelerometer.

A piezo-resistive accelerometer consists of a mass, connected to a frame by beams, which can be represented by a damped spring (see Figure 1.4). The accelerometer output carries two signals: a signal related to the acceleration of movements and a gravity-related signal, which is related to the position of the accelerometer relative to gravity (see Figure 1.4). When there is no movement, the accelerometer signal exclusively reflects the component related to the orientation of the accelerometer with respect to gravity. However, when there is movement, the orientation component and acceleration component will change simultaneously. Both signals can be distinguished by using at least 9 uniaxial accelerometers on each segment (Mital and King. 1973; Hayes et al. 1983; Van den Bogert et al., 1996). Another option to distinguish linear acceleration from the gravity related component is to add gyroscopes to the accelerometers. Gyroscopes measure the angular velocity based on the Coriolis principle. These combined systems appear to be very accurate in assessing the orientation of a segment and thus angular velocity and angular acceleration (errors smaller than 7% for angle, angular velocity and angular acceleration have been reported) (Luinge et al., 1999; Mayagoitia et al., 2002). All these solutions to distinguish the two components of accelerometer signal have the disadvantage that more sensors have to be added resulting in more wires and larger devices to store the signals. This will lead to discomfort for the subject.

Dyskinesia occurs in the neck, face, trunk or limbs. PD patients with mild dyskinesia commonly suffer from dyskinesia in only one of these body segments. However, the body segment that is dyskinetic can vary over time. Therefore, movement sensors have to be placed on various body segments for a successful and complete detection of LID. However, a large number of body segments results in discomfort for patients due to the large number of sensors. These sensors are tethered to a portable recorder, which is also worn by the

patient. For this reason, the number of sensors on a segment and also the number of segments that can be measured is limited. Because movements of body segments are in three dimensions, three orthogonal placed accelerometers on each segment would be best. In chapter 2 we have used a device that was able to store signals of 8 sensors. In that study 2 uniaxial accelerometers were placed on the wrist, upper arm, trunk and leg. In chapters 3 and 4, an ambulatory recorder that was able to store signals of 24 different uniaxial sensors was used. In that study, six sets of three orthogonal accelerometers were placed at both upper arms, both upper legs, at the wrist of the most dyskinetic side, and at the trunk. Figure 1.5 shows the ambulatory recorder with a triaxial accelerometer used to collect the data described in chapter three and four.

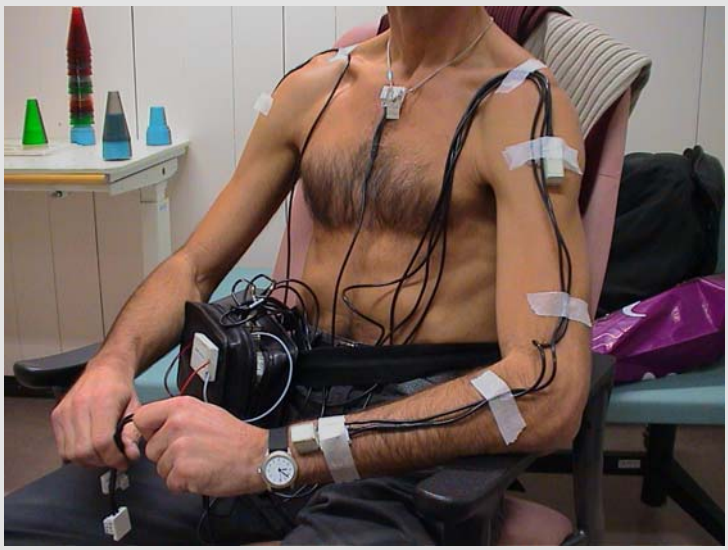

Figure 1.5. The ambulatory recorder and accelerometers attached to a subject as used in the studies described in chapter 3, 4, and 5.

Analysis of sensor signals

In Parkinson's disease, an automatic ambulatory assessment has to be able to distinguish between various motor states. At present, several studies have focused on the assessment of a single motor state or a particular symptom of Parkinson's disease in daily life. However, in the assessment of dyskinesia, it is important to discriminate between voluntary movements and levodopa induced dyskinesia. For example, peeling potatoes or washing dishes will result in many voluntary movements but these are not dyskinetic, although they may be intermingled with dyskinetic movements if the patients happens to be in a dyskinetic period. Therefore, the major challenge in assessing LID in daily life is to find movement characteristics that are able to distinguish LID from voluntary movements.

Another important issue in the development of quantitative methods is to test their validity. So far, the only gold standard of assessing the severity of dyskinesia is the assessment by a well-trained physician using standard rating scales. In this thesis, the

severity of dyskinesia is rated using the modified Abnormal Involuntary Movement scale (m-AIMS) (Guy, 1976). In this scale, the severity of dyskinesia is rated on a five-point scale between 0 and 4 for each of the four limbs and the trunk separately. Zero implies no dyskinesia and four implies extreme dyskinesia.

The next step in developing a device to assess the severity of LID is to find an algorithm that uses the accelerometer signals to rate the severity of dyskinesia. For this purpose, linear classification techniques have most commonly been used to evaluate the validity of a new quantitative measurement. Linear classification techniques are sometimes sufficient in controlled settings when only a simple motor disorder is involved. However, voluntary movements often show characteristics that interfere with characteristics of the movement disorder. In addition, relations between clinical rating and various movement parameters are usually not known and these relations can be highly nonlinear. Therefore, linear classification techniques are often not sufficient for a proper detection and assessment of motor disorders (French et al., 1997). In this context neural networks have proven to be very successful since they can be trained to detect and assess the severity of dyskinesia even when no explicit rules and relationships are available for proper classification, and as long as data are available to train them (Hertz et al., 1991; Kappen and Gielen, 1997).

Neural networks are mathematical models that use learning algorithms inspired by the brain to store information. Similar to the brain, neural networks are built up of many neurons with many connections between them. Neural networks have been used in many applications to model unknown relations between various parameters based on a large number of examples. Examples of successful applications of neural networks are classification of handwritten digits, speech recognition and the prediction of the stock prices. Many different types of neural networks exist. Examples of various types of neural networks are the Hopfield network, the multilayer perceptron, the Boltzmann machine and the Kohonen network (see Hertz et al. (1991) for an overview). In this thesis, only the multilayer perceptron was used.

A multilayer perceptron consists of a number of layers containing one or more neurons (see Figure 1.6 for an example). The role of the input neurons (input layer) is to feed input patterns into the rest of the network. After this layer there are one or more intermediate layers of units (hidden layers), followed by a final output layer where the result of the computation is read off. Each unit is connected to all units in the subsequent layer and each unit receives input from all units in the previous layer. Each connection has a certain weight, and this weight illustrates the influence of the unit to the response of the unit in the subsequent layer. The output of a multilayer perceptron depends on the input and on the strength of the connections of the units. When information is offered to a multilayer perceptron by activating the neurons in the input layer, this information is processed layer by layer until finally the output layer is activated. Given enough hidden units and enough data, it

has been shown that multilayer perceptrons can approximate virtually any function to any desired accuracy. In other words, multilayer perceptrons are universal approximators. However, these results are valid if and only if there is a sufficiently large number of training data in the series. If there are not enough data to “train” the neural network, the network will not be able to learn the required input-output relationship accurately. Therefore, multilayer perceptrons are valuable tools to solve complex problems when sufficient data are available to train them.

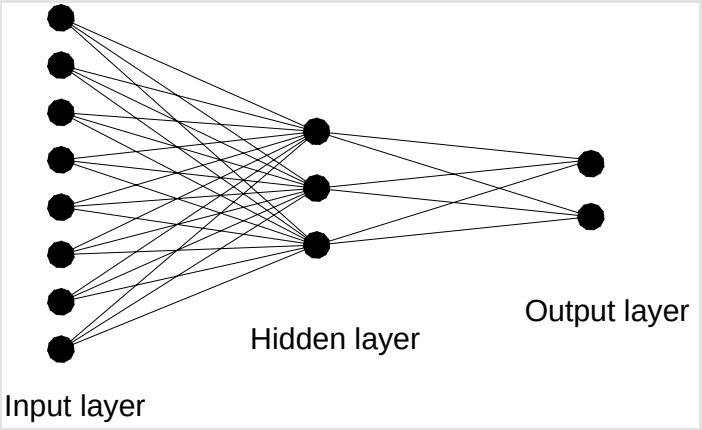

Figure 1.6 A multilayer perceptron with 8 neurons in the input layer, 3 neurons in the hidden layer and 2 neurons in the output layer.

In many respects, the learning process (training) of a neural network is rather similar to the way the brain learns to distinguish certain patterns from others. The learning process of a neural network proceeds by way of presenting the network with a training set composed of input patterns together with their corresponding desired output pattern. By presenting we mean that a certain pattern is fed into the input layer of the network. We start off with a network with random connections between the neurons, which gives a random output for a given input. We then train the network by presenting it with successive patterns drawn from an example set, which is typical of the problem we want the network to work on. For each of these patterns, we look at the output pattern the network gives us and compare it with the output we would ideally like. By comparing the output of the network with the target output for that pattern we can measure the error the network is making. This error can then be used to alter the connection strengths between layers in order that the network's response to the same input pattern will be better the next time. In other words, the purpose of the training process is to minimize the error between the desired output and the neural network output by adjusting the weights between units of subsequent layers. The training of a network is commonly done by a procedure called backpropagation. Backpropagation modifies the strengths of the connections between a layer and the previous layer starting with the output layer based on the error between desired and actual output of the network. The network

processes the records in the training data one at a time, using the weights and functions in the hidden layers, and then compares the resulting outputs against the desired outputs. Errors are then propagated back through the system, causing the system to adjust the weights for application to the next record to be processed. This process occurs over and over as the weights are continually tweaked. During the training of a network the same set of data is processed many times as the connection weights are refined.

The architecture of a neural network plays a critical role in whether or not it can be trained to learn a particular set of data. The question of how many nodes and connections to have in a neural network cannot be answered easily. There are many ways to approach this problem. Clearly, the simpler the architecture, the simpler a function the neural network is computing. Too simple an architecture will result in a network that cannot learn to approximate a complex function. A too complex architecture has been shown to result in a network losing its generalization capability. The generalization capability is the performance of a network to give a proper classification for new input pattern, which the network has not encountered before. Generalization is an important feature to maintain in order to avoid overfitting. Overfitting happens in case of a small training set, in which case the network cannot distinguish between information in the patterns and the noise. The consequence is that the network learns noise, rather than the general characteristics in the data-base. The generalization performance of a network can be evaluated by training the network with a part of the whole data set (for example 80 % of the data, which is called the training set) and testing the trained network with the remaining data that was not used for training the network (for example 20 % of the data, which is called the test set).

Deficiency in sensory processing

As already mentioned in the general introduction, PD symptoms are a consequence of Dopaminergic cell loss in the Substantia Nigra, which is part of the Basal Ganglia. As a result of this Dopaminergic cell loss in the substantia Nigra, the basal ganglia starts to dysfunction. So far, research has mainly focused on motor disorders like tremor, hypokinesia and bradykinesia that are a result of the dysfunction of the basal ganglia. However, more recent studies suggest that PD patients have some deficits in the processing of sensory inputs and particularly in the processing of proprioceptive inputs. For example, PD patients were less sensitive in identifying the occurrence and direction of externally imposed movements (Schneider et al., 1987). Furthermore, PD patients produce larger errors than controls in static joint position sense of the elbow (Zia et al., 1999). Also, PD patients make larger errors than normal subjects in reproducing a passive finger movement (Jobst et al., 1997) and make larger errors in matching the position of a passively moved finger to the position of a visual target (Klockgether et al. 1995). In addition, PD patients had an abnormal reduction in the degree of undershoot of slow voluntary movements when antagonist

muscles were vibrated (Rickards et al., 1997; Khudados et al., 1999). An explanation for these findings is that PD patients have a defective peripheral kinesthetic feedback, either because the afferent information itself is flawed or because the information, although accurate, is abnormally processed at a central level. Because muscle spindle sensitivity is normal in PD (Delwaide and Gonce, 1993), the impaired joint position sense in PD seems primarily of central neural origin. This hypothesis is supported by the finding of reduced sensory-evoked brain activations in cortical (parietal and frontal) and subcortical (basal ganglia) areas in PD patients using positron emission tomography (Boecker et al., 1999). Furthermore, a reduced level of intracortical inhibition was found in PD patients, which also suggested an abnormal influence of afferent input on corticomotor excitability (Lewis and Byblow, 2002). In addition to findings in PD patients, Filion et al. (1988) reported an increase in the number, magnitude, and loss of specificity of responses in the basal ganglia of MPTP monkeys to passive limb movement. Therefore, the deficits in motor performance in PD may, at least partly, be due to deficits in the processing of sensory (mainly proprioceptive) information in the basal ganglia.

Because PD is a progressive neurodegenerative disease, we postulate that deficits in the processing of sensory information in PD depend on the severity of the disease. Animal studies have shown that the ability to use sensory information depends on the degree of dopamine deficits in the substantia Nigra (Cools, 1993; Martens et al., 1996). A minor dopamine deficit in the caudate nucleus only affects its first output station, the substantia nigra, pars reticulata. Animals with such a minor dopamine deficit showed a reduction of the ability to use static proprioceptive stimuli in motor control (Cools et al., 1983; Jaspers et al., 1984, 1989). Such animals could only switch from one motor program to another when external sensory cues were available to direct their movement. Therefore, proprioceptive information processing was affected following minor dopamine deficits, but this could be overcome with the use of visual information. The need of visual cues is also illustrated in daily life. PD patients often adopt a stooped posture with their heads down during rest or need visual cues to start a movement. The stooped posture will disappear when they see themselves in a mirror (visual cue) or when they start to move. In addition, PD patients have benefit of visual cues to initiate a movement (Morris et al., 1994; Praamstra et al., 1998; Azulay et al., 1999, 2002; Lewis et al., 2000). More severe dopamine deficits in the Substantia Nigra produce a GABA hyperactivity in the deeper layers of the Colliculus Superior (Scheel-Kruger, 1985). Animals with a (mild) GABA hyperactivity in the Colliculus Superior showed a reduced ability to use external visual information in switching between motor patterns (Gelisssen and Cools, 1986; 1987a,b; 1988). Extrapolating these results to humans suggests that in an early stage of PD (a mild dopamine deficit), patients will have more difficulty than age-matched controls in performing tasks in a condition without visual information. In a condition where visual information is available, our hypothesis is that mild

PD patients may be as accurate as age-matched controls. However, with ongoing progression of PD, patients might have more difficulty, even in conditions with visual information.

The role of visual and proprioceptive information processing can well be tested in accurate movements to external targets, for example in pointing to remembered targets (Soechting and Flanders, 1989a,b; McIntyre et al., 1997; Messier and Kalaska, 1997). Errors in these pointing movements may be caused by a failure in spatial memory or may be due to problems with sensory input processing. It was shown that PD patients and controls do not reveal significantly different errors in pointing to a remembered visual target with a Light-Emmiting-Diode on their pointing fingertip in complete darkness (Adamovitch et al., 2001) and with visual feedback (Poizner et al., 1998). This was interpreted as evidence that PD patients have adequate spatial memory to achieve normal accuracy during pointing movements (Poizner et al., 1998; Adamovich et al., 2001). Therefore, PD patients will most likely experience difficulty with pointing movements as a result of the inability to use sensory information. For these reasons, the accuracy of pointing movements in PD patients will most likely depend to a large extent on the availability of visual and proprioceptive information.

Several studies have investigated the role of visual and proprioceptive information by asking subjects to point to visual or to remembered visual targets (Soechting and Flanders, 1989a,b; McIntyre et al., 1997; van Beers et al., 2002). When pointing to remembered visual targets in complete darkness, proprioceptive information is the most reliable source of information for the accuracy of the motor system (van Beers et al., 1999, van Beers et al 2002). With visual feedback of finger position, the accuracy of pointing increases, especially in azimuth and elevation and to a lesser extent in depth (depth refers to radial direction of the observer) (van Beers et al., 2002). In chapter 6 of this thesis, the role of proprioceptive and visual information on pointing to remembered visual targets in PD will be evaluated. PD patients and age-matched controls are studied under two conditions: pointing to a remembered visual target in complete darkness and in the presence of an illuminated frame with a continuously lit red LED attached to the tip of the index finger. In complete darkness, subjects have to rely on proprioceptive information, whereas they can also use visual cues in the condition with the illuminated frame. The effect of disease severity will be evaluated by studying patients with a range of disease severity.

Outline of thesis

Chapter 2 evaluates the feasibility of artificial neural networks in assessing and rating the severity of LID using the data obtained by Hoff and coworkers (2001a). In this study by Hoff and coworkers (2001a), patients were tested in a limited set of seven daily life tasks of one-minute duration each. Hoff et al. (2001a) used a linear discriminant analysis on these data to assess the severity of dyskinesia for tasks in which patients abstained from voluntary

movements. They had problems in assessing the severity of LID when voluntary movements were present, such as during drinking and walking. The purpose of our study was to evaluate whether neural networks could provide a better distinction between LID and voluntary movements.

The results in Chapter 2 were considerably better than those obtained by Hoff et al. (2001a). Yet, they were far from optimal, indicating that considerable improvement is needed to obtain a reliable method that can be used to assess dyskinesia in daily life. One of the reasons for this may be related to the limited set of tasks in which patients have been tested. Therefore, we tested patients with Parkinson's disease with various degrees of LID in a large variety of daily life activities for a period of a few hours in a natural environment. The results of this study are described in Chapter 3.

The excellent performance of the neural network in chapter 3 raises the question whether it would be possible to obtain insight in the various parameters used by the neural network to assess the severity of dyskinesia. This is important for two reasons. The first reason is that acceptance of a new technique will be easier if physicians, who will use the technique, do understand why it is successful. The other reason is that insight in the movement parameters, which underlie pathological behavior, might be valuable for understanding normal behavior. In Chapter 4, the behavior of the optimal neural network and the relevant movement parameters and their relation to the severity of LID were analyzed.

Chapter 5 provides an example of using the neural network for evaluating the effect of medication on the severity of dyskinesia. Verhagen et al. (1997) found that incrementing the levodopa doses higher than 1.5 times the threshold dose (up to 3 times) did not further increase the severity of dyskinesia. In this study patients were studied in a stable psychomotor state and environment and the severity of dyskinesia was assessed using clinical rating scales. Normally, dyskinesia is clearly evoked by mental activity, stress, and social interactions with other persons. For these reasons, the results found in the study of Verhagen et al. (1997) could be a result of the environmental setup and/or the assessment of dyskinesia. In chapter 5, the method developed in chapter 3 and 4 was used to assess the severity of dyskinesia of patients who were given three different doses of levodopa medication (1, 1.5 or 2 times the usual levodopa dose of the particular patient). This study tested the hypothesis that incrementing the levodopa dose higher than 1.5 times the threshold will not further increase the severity of dyskinesia in a more natural setting.

In chapter 6, patients with Parkinson's disease and age-matched controls were tested in pointing to remembered visual targets in complete darkness and in the presence of an illuminated visual reference frame. The effect of disease severity was evaluated by studying patients with a range of disease severities.

Chapter 7 presents a summary on the content of this thesis.

Detection and Assessment of the Severity of Levodopa Induced Dyskinesia in Patients with Parkinson's Disease by Neural Networks

Adapted from: Keijsers NLW, Horstink MWIM, Gielen CCAM. Mov. Disord. 15:1104-1111, 2000.

INTRODUCTION

With each year of Levodopa treatment, the number of patients with Parkinson's disease who suffer from drug-induced dyskinesias, increases (Nutt, 1990; Hortsink et al., 1990a,b; Marsden, 1994; Nutt et al., 1995; Lang and Lozano, 1998a,b). The actual emergence of Levodopa-induced dyskinesia (LID) throughout the day depends on the timing and quantity of each individual dose of Levodopa. Therapeutic strategies aiming to reduce LID will benefit from adequate assessment of LID in relation to the dosing schedule. However, methods to assess LID are scarce and operate in a semi-quantitative way (Fahn and Elton, 1987; Goetz et al., 1994; Hoff et al., 1999). Moreover, these semi-quantitative methods are subjective and may lack responsiveness. Self-assessment of dyskinesias by patients is most frequently used in clinical practice but can be troublesome and unreliable for some patients (Golbe and Pae, 1988). For these reasons, an automatic and more quantitative method to assess LID would be useful.

Continuous ambulatory multi-channel accelerometry (CAMCA) is now successfully applied in the assessment of hypokinesia, bradykinesia and body position in PD patients (Dunnewold et al., 1998). Based on velocity and amplitude within particular frequency bandwidths of movements recorded with CAMCA, LID was reliably assessed for conditions in which patients abstain from voluntary movements (Hoff et al., 2001a). Burkhard et al. (1999) used frequency analysis of a rotation-sensitive movement monitor (RoMM) and found it a valid, reliable, and sensitive method to quantify and characterize dyskinesia. However, both studies (Hoff et al., 2001a; Burkhard et al., 1999) were not able to distinguish voluntary movements from dyskinesias in daily life. Therefore, it is necessary to find specific parameters and classification techniques, which give an objective characterization of LID in daily-life activities and which can be obtained automatically.

We evaluated the feasibility of artificial neural networks in distinguishing LID from voluntary movements and in the assessment of dyskinesia severity using the data obtained in a previous study by Hoff et al. (2001a). Neural networks have the advantage that they can be trained to distinguish LID from voluntary movements in PD and to assess the severity of LID, even when no explicit rules are available for proper classification, as long as data are available to “train” these neural networks. Artificial neural networks can be more accurate than linear statistical methods because they learn to recognize the critical nonlinear interactions among variables and then weight this information to predict a given outcome (French et al., 1997). For a good review of neural networks, see Hertz et al. (1991).

The purpose of this study was to use artificial neural networks for the classification of movements in patients with PD for the assessment of LID. First, neural networks were used to rate the severity of LID in a particular task, similar to the regression analysis in the study by Hoff et al. (2001a). The second aim of this study was to explore the ability of neural

networks to detect and to classify LID in a large repertoire of movement tasks.

METHODS

Patients and data acquisition

Sixteen patients were examined at the time of the day when they normally suffered from LID. During the test, the patients showed various degrees of severity of LID while occasionally LID did not occur. Patients who did not develop LID during some of the sessions provided the opportunity to distinguish between LID and voluntary movements.

Each patient was tested in a laboratory setting in which he or she performed in seven different 1-minute tasks. The first task consisted of sitting in a chair abstaining from any voluntary movement, while the patient was asked not to suppress any involuntary movements. For tasks 2 and 3 patients were sitting in a chair with the instruction to count forward or to spell a predefined set of words backward, respectively, resulting in an increase in LID caused by the influence of stress (Hoff et al., 2001a). Tasks 4 to 7 belonged to the tasks of the Dyskinesia Rating Scale (DRS), namely drinking from a cup (task 4), putting on a coat (task 5), buttoning a shirt (task 6), and walking (task 7) (Goetz et al., 1994). The behavior of all patients in these tasks was videotaped. The videotapes were used to assess the severity of dyskinesia by two experienced clinical researchers using the modified Abnormal Involuntary Movement Scale (m-AIMS) (Hoff et al., 1999; Hoff et al., 2001a; Guy, 1976). In this scale, the severity of dyskinesia is rated on a five-point scale between 0 and 4 for each of the four limb segments and the axis separately (0 implying no dyskinesia and 4 implying extreme dyskinesia).

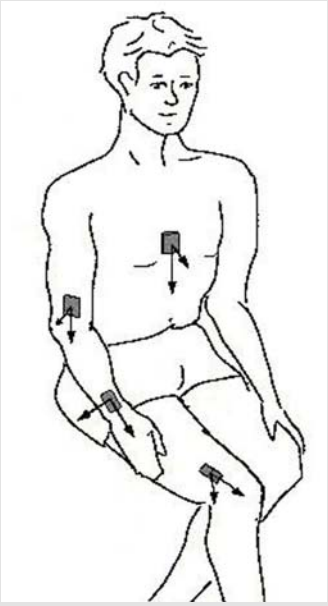

Figure 2.1. Accelerometer positions on the body. The two directions for measurement of acceleration by each set of accelerometers is indicated by arrows.

Posture and movements were measured by 8 piezo-resistive Uni-axial accelerometers (IC Sensors, model 3031) attached in orthogonal pairs (tangentially and radially) to the wrist, the upper arm (just above the elbow joint), the trunk (on the sternum) and the leg (just above the knee joint) of the most affected side (see Figure 2.1). The accelerometers were placed on each body segment to measure the movement in a sagittal plane (extension and flexion) and in a frontal plane (abduction and adduction) (see Figure 2.1). The accelerometer signals were digitally sampled at a rate of 32Hz and stored on a Vitaport recorder (Vitaport, Cologne, Germany).

Data analysis

Because of the limited data and the wish to obtain better insight into the results, the accelerometer signals of a trial were preprocessed before being presented to the network. This preprocessing resulted in 38 parameters for each task for each patient. Figure 2.2 shows a schematic view of the data analysis, which is described in the following two sections.

Preprocessing of Accelerometer Signals

The raw signal obtained in the study by Hoff et al. (2001a) from each accelerometer was filtered by a second-order low-pass digital Butterworth filter with a 3-dB cut-off frequency at 8Hz, because higher frequencies were considered to be irrelevant for the detection and classification of LID. Each accelerometer signal carries two signals: a signal related to acceleration of the limb and a signal related to the position of the limb relative to gravity. These two signals cannot be distinguished. Because any changes in the accelerometer signal reflect movements of the body segment, the derivative of the accelerometer signal will be referred to as “velocity”. However, this strictly only refers to the derivative of the position related component since the derivative of the acceleration component is jerk (third derivative of position), rather than velocity. For each body segment, segment velocity (*V segment*) was defined as the square root of the sum of squares of the derivatives of the two accelerometer signals from that body segment.

For each of the four body segments the following eight parameters were calculated using their segment velocity in each of the seven tasks for offline training of the neural network: (1) the mean segment velocity ($\overline{V}$ *segment*), and (2) the standard deviation, $SD(V)$ *segment*, of the segment velocity; (3) the percentage of time that the segment velocity was above a particular threshold (see below) ($\%V_\theta$ *segment*) and (4) the mean velocity ($\overline{V}_\theta$ *segment*) in the time intervals when the velocity exceeds this particular threshold. Each accelerometer signal has a certain noise, which contributes to noise in the segment velocity. For each body segment, the particular velocity threshold was set at the level of five times the noise in the segment velocity, which is defined as the standard

deviation of the signal when the limb segment is at rest. (5) The mean value of the auto-correlation for the segment velocity over time ($\overline{\rho}_{segment}$). The autocorrelation is thought to be useful, because the mean value of the autocorrelation function provides a measure for the amount of movement per unit of time, which is expected to be large for LID.

The segment velocity was evaluated in two frequency domains, namely for frequencies below and above 3 Hz. The mean velocity in each of these frequency domains ($\overline{V}_{<3Hz}$ *segment* , $\overline{V}_{>3Hz}$ *segment*) and their ratio ($\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *segment*) were used as parameters six, seven, and eight, respectively. These eight parameters were calculated for each body segment separately.

In addition, the maximal values of the normalized cross-correlation between the velocity signals for all pairs of the four body segments ($\max(\rho_{segment-segment})$) were calculated and resulted in another six parameters. The cross-correlation between body segments gives an indication of the correlation between movements of different segments. Healthy people show a high correlation between upper arm and forearm movement and between arm movements and trunk movements (Soechting et al., 1986; Gielen et al., 1997). Therefore, voluntary movements are expected to give high values for the cross-correlation. LID movements of different limb segments give the impression to be uncorrelated and are expected to provide small values for the cross-correlation. Hence, eight different parameters for each of the four body segments result in 32 parameters plus the six cross-correlations between movements of the four body segments, resulting in 38 parameters in total.

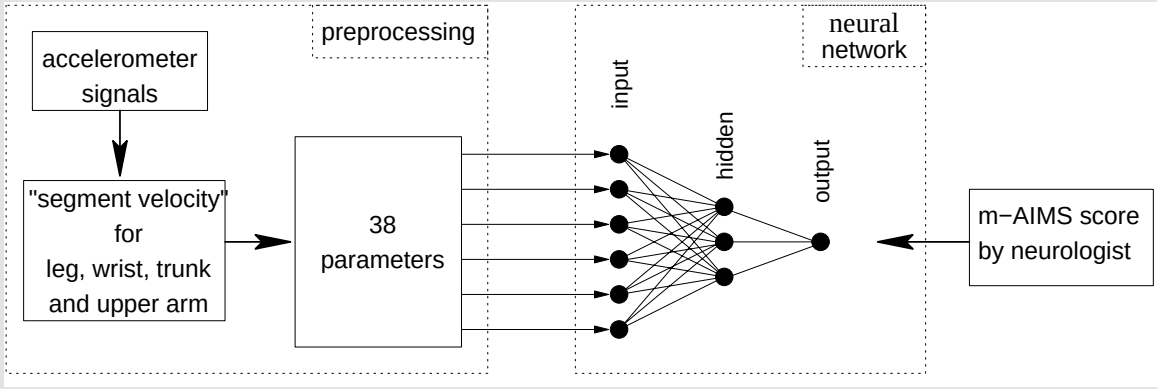

Figure 2.2. Data analysis with a preprocessing part and a neural network part. In the preprocessing stage, the raw signals of the accelerometers on wrist, upper arm, trunk and leg are transformed to 38 parameters. The neural network maps the parameters (input) to the rating by the neurologist (output) by adjusting the connections between units in subsequent layers.

Neural network

Neural networks have been successfully applied for a wide range of pattern recognition and classification problems (Kiani et al., 1998; Kappen and Gielen, 1997). The

neural network used in this study was the Multilayer Perceptron (MLP) with an input layer, one hidden layer, and an output layer. Each layer exists of a number of units and each unit is connected to all units in the next layer. Figure 2.2 shows a neural network with an input layer with six units, a hidden layer with three units, and an output layer with one unit. Each connection has a certain weight and this weight illustrates the influence of the unit to the response of the unit in the subsequent layer. The input hi of a unit i in a hidden or output layer is the weighted summation of all input signals to that unit. The output of the unit is given by a sigmoid transfer function that gives a value between 0 and 1 ($f(h_i) = 1/ (1 + e^{-hi})$). As in many other pattern recognition methods, artificial neural networks need a set of training data, which provide examples how input variables are related to output variables. A collection of many of these examples is used to train the network. This training process implies that the weights between units of subsequent layers are adjusted in order to minimize the error between the desired network output (measured output) and the neural network output for each set of input variables. Each pass through the data increases the model's accuracy as the actual outcome is compared with the predicted outcome, so the system learns by trial and error. The training process was done using the backpropagation algorithm (Hertz et al., 1991). Backpropagation modifies the strength of the connections based on the error in each pass to increase the accuracy in subsequent passes.

Any subset of the 38 parameters, which was derived from the accelerometer signals on the four body segments, could be used as input variables. The choice of the number of input units and the parameters used was dependent on the particular task of the network and will be specified in detail later. The output layer has only one output unit, which represents the severity of LID on the m-AIMS scale of a particular body part (arm, leg, or trunk). Because the output of the unit has a value between 0 and 1, the output values of 0.1, 0.3, 0.5, 0.7 and 0.9 were used to represent the m-AIMS scores 0, 1, 2, 3 and 4, respectively.

The number of units in the hidden layer is crucial for the ability of the network to generalize. A good generalization means that the network is able to give a proper classification for an input pattern, which the network has not encountered before. The optimal number of units in the hidden layer and thus for optimal generalization is the number of units that gives the smallest error on a test set, which the network has not encountered before. The optimal number of units appeared to be one for each network that was developed in this study.

Data evaluation and statistics

The first aim of this study was to investigate whether neural networks provide a valid method to detect and to rate the severity of LID in patients with PD for a particular task. The validity of neural networks to classify the severity of LID was evaluated using two different criteria. The first criterion used was the mean error between the neural network output and

the actual m-AIMS score. The second criterion was the Spearman correlation between actual m-AIMS score and the neural network output. We also explored which combination of parameters was most informative to match the rating by the neurologists for each task and for each body-part (arm, leg, and trunk). The best parameter combination was selected as the minimal set of parameters, which gave the smallest mean error between the neural network output and the actual m-AIMS score. For this purpose, a neural network was trained for each task and for each body part with the data of all patients, and this particular trained network was then used to rate the severity of LID on the m-AIMS scale for that task and that body part for each patient.

Besides the validity of the neural networks to classify the severity of LID, it is important that the neural network is able to generalize, that is, to give a proper classification of LID for data that the network has not encountered before. This means that a trained network should be able to rate the severity of LID for a new patient in a given task properly by using the accelerometer signals in that task for that subject. The ability of generalization was tested with the “leave-one-out” method. For each particular task, the leave-one-out method implies that for each patient the severity of LID was predicted by a neural network, which was trained with the data of the other 15 patients. The mean error between all the 16 “predicted” m-AIMS scores by the 16 different trained neural networks and their actual m-AIMS scores by the neurologist was used as a measure for the generalization performance of the network. The Spearman correlation between the actual m-AIMS score and the predicted m-AIMS was also used to evaluate the generalization of the network.

For practical purposes, any classification algorithm should be able to operate in daily life activities and thus should be able to distinguish LID from voluntary daily life activities and, if present, to assess the severity of LID with unsupervised, automatic techniques. Therefore, we have also used neural networks to classify movements on the m-AIMS scale without prior knowledge of the task in which patients were tested. For this purpose, the data from all seven tasks obtained in all sixteen patients were combined to one data set (a total set of 112 trials) and were used to train the neural network. By combining the data of all tasks and all patients the data set includes relaxed postures, voluntary movements without LID, voluntary movements with LID and plain LID. A good classification will rate a relaxed posture or voluntary movements with a score 0, whereas any amount of LID during the voluntary movements will result in a score larger than zero, up to 4 for the most severe LID. The validity of the neural network to classify LID in various daily activities was determined by the mean error and the Spearman correlation in the same way as described before. Different neural networks were trained for arm, leg and trunk and the ability of generalization in various daily activities was also explored. For this purpose, generalization was also tested with the leave-one-out method, which implies that the neural network was trained with 111 trials of data and that the rating for the remained 112th trial was predicted by the trained

network. The neural network was trained with all 38 input parameters as input. Because of the relatively small number of examples (112 trials and only seven different tasks), using all 38 parameters for input could lead to an overfitting of the data and thus to a bad generalization performance of the neural network (Hertz et al., 1991). Therefore, other neural networks architectures with fewer input units were analyzed and the architecture with the smallest mean error for the leave-one-out method (best generalization) will be described in the results session.

RESULTS

Detection and Rating of LID in a Particular Task

First we have trained 21 neural networks to classify the severity of LID, one for each of the 3 body parts (arm, leg, and trunk) and for each of the 7 tasks. The best performance was obtained using the mean segment velocity of a body part and the cross-correlation of that body part with a connecting body segment as input to the neural network. For the arm, where movements of two segments were measured, the mean segment velocity of the wrist ($\overline{V}_{wrist}$) was used together with the cross-correlation between the segment velocity of upper-arm and wrist ($\max(\rho_{upper\ arm-wrist})$). For the leg we used the mean segment velocity of the leg ($\overline{V}_{leg}$) and the cross-correlation between the segment velocity of leg and trunk ($\rho\max(\rho_{leg-trunk})$). For the trunk we used the mean segment velocity of the trunk ($\overline{V}_{trunk}$) and the cross-correlation between the segment velocity of the upper arm and trunk ($\max(\rho_{trunk-upper\ arm})$). The Spearman correlation and mean error between the output of

Table 2.1. Performance of the trained neural network for different tasks

	Arm		Leg		Trunk	
Task	R_s	ME	R_s	ME	R_s	ME
Sitting	0.89**	0.37	0.89**	0.35	0.88**	0.32
Counting	0.88**	0.46	0.91**	0.47	0.95**	0.37
Spelling	0.94**	0.48	0.93**	0.39	0.94**	0.40
Drinking	0.82**	0.51	0.96**	0.34	0.89**	0.47
Putting on a coat	0.81**	0.33	0.86**	0.50	0.91**	0.49
Buttoning	0.84**	0.32	0.76**	0.51	0.90**	0.60
Walking	0.75**	0.49	0.66**	0.62	0.51*	0.47

Spearman correlation between the trained neural network output and the actual m-AIMS score R_S and mean error between the trained neural network output and the actual m-AIMS score (ME) for the 7 tasks for each body-part with $\overline{V}_{segment}$ and $\max(\rho_{segment-segment})$ as input features. *=significant correlation with p<0.05; **=significant correlation with p<0.01

the neural network and the m-AIMS score for the arm, leg, and trunk are shown in Table 2.1. The mean error values were small and the Spearman correlation between neural network output and actual m-AIMS scores was significant for all tasks and for all body parts. The Spearman correlations were significantly higher than those obtained with linear regression techniques in the previous study (Hoff et al., 2001a) (see Discussion).

The generalization performance of the neural network for a given task, that is, the ability of the network to detect and to rate LID for new patients, was determined using the leave-one-out method. The Spearman correlation and mean error values for the leave-one-out method for the network with two input units receiving $\overline{V}$ *segment* and ρs-s as input for each body part are shown in Table 2.2. The results for generalization are slightly less than those for the training method. However, the network showed a significant correlation between neural network output and the actual m-AIMS score for most tasks, except for the trunk and leg for walking (Table 2.2). The implications of these results will be elaborated in the discussion.

Table 2.2. Performance of the "predicted" neural network output

	Arm		Leg		Trunk	
Task	R_s	ME	R_s	ME	R_s	ME
Sitting	0.76**	0.51	0.65**	0.50	0.76**	0.51
Counting	0.74**	0.58	0.63**	0.76	0.89**	0.48
Spelling	0.90**	0.57	0.89**	0.50	0.90**	0.51
Drinking	0.60*	0.86	0.91**	0.46	0.67**	0.64
Putting on a coat	0.62**	0.51	0.77**	0.71	0.81**	0.70
Buttoning	0.75**	0.63	0.65**	1.26	0.78**	0.88
Walking	0.67**	0.81	0.00	0.96	0.07	1.09

Spearman correlation between the "predicted" neural network output and the actual m-AIMS score R_S and mean error between the "predicted" neural network output and the actual m-AIMS score (ME) for the 7 tasks for each body-part for patients not included in the training set (leave-one-out method) with $\overline{V}$ *segment* and $\max(\rho_{segment-segment})$ as input features. *=significant correlation with p<0.05; **=significant correlation with p<0.01

Detection and Rating of LID in Various Daily Activities

For the second and more important purpose for practical applications, all data of all tasks and all patients were combined. For this purpose, new neural networks were trained which had to distinguish LID from voluntary movements and to assess the severity of LID without previous knowledge about the task for various patients. For the network with all 38 parameters as input, the mean error was small and the Spearman correlation was high for

the training method (Table 2.3). The best generalization performance was found for the network with the following 16 input units: the mean segment velocity ($\overline{V}$ *segment*), the percentage of time that the segment velocity exceeds a particular threshold ($\%V_\theta$ *segment*), the mean segment velocity of movement components above 3 Hz ($\overline{V}_{>3Hz}$ *segment*) and the autocorrelation ($\overline{\rho}_{segment}$) for each of the four body segments. The performance of the training method and the generalization of the network with these 16 parameters as input are also shown in Table 2.3. The data in Table 2.3 show a high Spearman correlation, indicating a good performance in the detection and rating of LID in various daily activities without any previous information about the task.

Table 2.3. Performance of the neural network for all tasks

	Training method					
Network	Arm		Leg		Trunk	
architecture	R_s	ME	R_s	ME	R_s	ME
38 input units	0.85**	0.48	0.95**	0.32	0.92**	0.35
16 input units	0.76**	0.60	0.90**	0.46	0.86**	0.54
	Leave-one-out method					
38 input units	0.58**	0.66	0.69**	0.86	0.71**	0.88
16 input units	0.64**	0.73	0.69**	0.67	0.73**	0.74

Spearman correlation R_s and mean error (ME) values for all tasks and all patients (112 sets) using the training method and leave-one-out method for the 3 different body-parts for the network architectures with 38 input units (see text) and the network architecture with 16 input units ($\overline{V}$ *segment*, $\%V_\theta$ *segment*, $\overline{V}_{>3Hz}$ *segment* and $\overline{\rho}_{segment}$ of each of the 4 body-segments), respectively. *=significant correlation with p<0.05; **=significant correlation with p<0.01.

DISCUSSION

Our results reveal a good performance of the neural network in distinguishing LID from voluntary movements and in the assessment of LID severity in various activities without prior information about the task or movement. The mean segment velocity ($\overline{V}$ *segment*), the percent of time that the segment velocity was above a threshold ($\%V_\theta$ *segment*), the mean segment velocity in frequencies above 3Hz ($\overline{V}_{>3Hz}$ *segment*) and the mean value of the autocorrelation ($\overline{\rho}_{segment}$) of each body segment emerged as the most important parameters used by the neural network to detect and to rate LID (Table 2.3). Additionally, the mean segment velocity ($\overline{V}$ *segment*) and cross-correlation ($\max(\rho_{segment-segment})$) proved to be sufficient to detect and to rate the severity of LID for a single body part. The regression analysis on the same data set in a previous study (Hoff et al., 2001a) failed in rating LID for

body parts involved in voluntary movements, like the arm in drinking. Neural network performance in detecting and rating LID was especially better for body parts involved in voluntary movements in comparison with the regression analysis (Hoff et al., 2001a). The Spearman correlation values for segments involved in voluntary movements for neural networks (0.82, 0.81, 0.84, 0.75, and 0.66) (Table 2.1) were significantly larger than that for the regression analysis in the study by Hoff et al. (2001a) (0.58, 0.59, 0.64, 0.77, and -0.01 for the arm for drinking, putting on a coat, buttoning, and walking and for the leg for walking, respectively).

Apparently, the approach of using only frequency analysis of accelerometer signals (Hoff et al., 2001a) or RoMM (Burkhard et al., 1999) mainly detects whether there is movement or not, whereas the neural network receiving the mean segment velocity and cross-correlation as input is able to distinguish between voluntary movement and LID except for walking (Tables 2.1 and 2.2). The relatively important role of the cross-correlation presumably reflects that movements of connecting body segments like upper arm and forearm, move independently in LID, whereas they move in a well-coordinated way in voluntary movements (Soechting et al., 1986; Gielen et al., 1997). The problem of rating the severity of LID for walking is presumably the result of the small number of patients. More data will give the opportunity to increase the number of input parameters without decreasing the generalization performance. Since walking is a periodic stereotyped movement, we expect that more data from more patients and adding new input parameters will enable the neural network to distinguish walking from LID, which corresponds to irregular movements of the legs.

To investigate how close the neural network performance could match the rating by physicians and thus to obtain an indication of the validity of the method, we calculated the mean error between neural network output and actual m-AIMS score. Since the m-AIMS score requires a physician to give an integer rating of 0, 1, 2, 3, or 4, while the neural network gives a continuous output, there will never be a perfect match. Assuming that output values of the neural network between 0.5 and 1.5 correspond to rating 1 and that the values between 1.5 and 2.5 correspond to rating 2 and so on, straightforward calculations predict a mean error of 0.25. This illustrates that mean errors near 0.5 (Tables 2.1-2.3) are actually good because it means that the difference between neural network prediction and m-AIMS rating is almost never larger than 1. This implies that if the neural network does not give the same rating as the physician, the rating is in a class next to that given by the physician. Although, the inter-subject variability between physicians in rating is rather small (Goetz et al., 1994; Hoff et al., 2000a), there will always be small differences between and within physicians due to the subjectivity of the rating scale. This will contribute to an increase in mean error between the output values of the neural network and the m-AIMS score given by the physicians. Therefore, based on the mean errors we conclude that neural networks are a

valid tool to detect and to rate the severity of LID.

The most important and difficult issue of automatic quantitative methods to assess LID in daily life is to distinguish voluntary movements from LID. By combining the data of all tasks and all patients the data set includes relaxed postures, voluntary movements without LID, voluntary movements with LID and plain LID. In spite of the difficulty of the task our relatively simple neural network architecture with 16 input units was able to detect and to rate the severity of LID and thus to distinguish LID from voluntary movements. The relatively small number of input units and the relatively simple architecture are presumably a consequence of the small number of training data in this study. When more training data become available from more subjects and in more movement conditions, the complexity of the neural network may have to increase providing even better performance to detect and to rate the severity of LID.

The data analyzed in this study were only for a number of particular tasks for a short period of time (1 minute) and in a laboratory setting. The ultimate challenge would be assessing the severity of LID during longer periods like a dose cycle. By combining the data of all tasks and all patients in this study, we tried to obtain a data set that looks more like a data set during a long period of time. A logical next step would be to study the possibility to assess the severity of LID of patients by using neural networks and accelerometer signals during a dose cycle or even during a day.

In conclusion, neural networks are a valid method to distinguish LID from voluntary movements and to classify the severity of LID. Further studies with more patients in a larger variety of natural movement situations will most likely lead to a more optimal architecture of the neural network and lead to a better performance of the neural network in the detection and classification of LID. This could finally lead to a more sensitive rating scale and a documentation of the severity of LID over time by an automatic quantitative assessment.

Automatic assessment of Levodopa induced dyskinesias in daily life by neural networks

Adapted from: Keijsers NLW, Horstink MWIM, Gielen CCAM. Mov Disord 18:70-80, 2003.

Introduction

Levodopa induced dyskinesia (LID) is a disabling and distressing complication of chronic levodopa therapy in patients with Parkinson's disease (PD) (Marsden, 1994; Nutt et al., 1995). Therefore, new pharmacological and surgical treatments to reduce these dyskinesias are of increasing interest (Brotchie, 1998; Manson et al., 2000b; Fraix et al., 2000; Lang, 2000; Rascol, 2000b). To evaluate medication and surgical treatment, it is important that dyskinesia can be assessed objectively in daily life. However, the commonly used methods to assess LID have several limitations (Goetz, 1999; Damier et al., 1999; Widner and Defer, 1999). For example, long term assessment by experts is not feasible as a routine procedure, and self-assessment of LID by patients can be unreliable (Golbe and Pae, 1988; Vitale et al., 2001). Moreover, the ratings are subjective. For these reasons, a portable device that can assess LID automatically and objectively in daily life would be highly useful (Brown and Manson, 1999).

Recently, several studies tried to find an objective and automatic method to assess dyskinesia using accelerometers, which can measure movements of patients without any discomfort (Burkhard et al., 1999; Hoff et al., 2001a; Keijsers et al., 2000; Manson et al., 2000a). Burkhard et al. (2000) used a rotation-sensitive movement monitor (RoMM) and could successfully quantify and characterize dyskinesia for patients who were asked to abstain from voluntary movements. In a study by Hoff and associates (2001a), patients were tested in a set of seven tasks of 1-minute duration each. These authors used a linear discriminant analysis and could assess the severity of LID for tasks in which patients abstained from voluntary movements. However, they had problems in assessing LID when voluntary movements were present, such as during drinking and walking. In our study described in chapter 2, we used the same data set as that used in the study by Hoff and colleagues (2001a) but used neural networks instead of linear discriminant analysis to assess LID. The neural network approach showed a better performance than the linear classification technique used by Hoff and associates (2001a), and also appeared to better distinguish between LID and voluntary movements. However, the results in chapter 2 were far from optimal, indicating that considerable improvement is needed in order to obtain a reliable method, which can be used in daily life. In another study, Manson and colleagues (2000a) attached a triaxial accelerometer to the shoulder and showed that the accelerations in the 1 to 3 Hz frequency band correlated well with the AIMS scale (Guy, 1976) for various tasks. Like in the previous chapter, Manson and coworkers (2000a) were able to assess the severity of LID, even when patients made voluntary movements. However, a main limitation in the study by Manson and colleagues (2000a) may be the low specificity for mild dyskinesias. Because all patients in that study suffered from severe dyskinesia during the test, the method was not validated to assess mild dyskinesias, which is important to evaluate

medication and surgical treatment.

This overview of methods for the objective assessment of LID illustrates that a successful method is not yet available. One of the reasons for this may be related to the limited set of tasks in which patients have been tested. The currently available algorithms for the assessment of LID were developed and applied to a small number of daily life activities, which were performed in a laboratory setting, each for a short duration (for example 1 minute). It may be that the data, collected in the small number of activities in these studies, did not contain enough information to provide an accurate measure to detect LID and to distinguish between LID and voluntary movements in daily life. If so, testing subjects over a longer period of time in a larger variety of activities might provide more and new information, which can be used by algorithms to detect and assess LID more accurately. Another improvement in classification performance may be obtained by recording movements in 3 orthogonal directions for various segments, because previous studies were limited to movements in two directions (Hoff et al., 2001a; Keijsers et al., 2000) or to measurement of movements of a single body segment (Manson et al., 2000a). In addition to an increased number of activities, testing patients in a natural environment for a long duration might provide more reliable data. A longer duration of testing will have the added advantage of showing various changing degrees of LID severity during the tests. This might provide insight into the movement variables, which allow a distinction between LID and voluntary movements.

We test patients with Parkinson's disease with various degrees of LID in a large variety of daily life activities for a period of a few hours in a natural environment to detect and assess the severity of LID. For the analysis of the data, we used neural networks that are known as adaptive techniques for complex classification problems and which can also provide valuable information on the movement variables that underlie a possibly successful detection and rating of LID.

Methods

Patients

Thirteen patients with Parkinson’s disease (8 men and 5 women) between 48 and 71 years old (mean, 61 ± 8 years) participated in this study. The patients had a mean duration of the disease of 15 ± 4 years (range, 10-21) and were on levodopa medication for several years. All patients suffered from LID. Mean levodopa medication was 692 ± 282 mg daily (range, 375-1375mg/day) and Pergolide medication was 2.2 ± 2.5 mg daily (range, 0-8mg/day). During the test all patients showed a variety of grades of severity of LID. Seven patients showed a severity of dyskinesia varying between no dyskinesia and mild dyskinesia

(rating between 0 and 1 on the AIMS scale). The other six patients showed a severity of dyskinesia varying between no dyskinesia to moderate (rating between 0 and 3 on the AIMS scale). The experiments were approved by the Medical Ethical Committee of the University Medical Center of the University of Nijmegen. The study started between 1200 and 1300 hours. The patients were continuously monitored for a period of approximately 2.5 hours. During this period, the patients took their regular medication at their usual time. However, when dyskinesia did not occur at the halfway point, extra levodopa was taken to induce dyskinesia.

The registration took place in a natural, home-like setting in the occupational therapy department of the University Medical Center. During the 2.5-hour monitoring session, the patients performed about 35 functional daily life activities, such as walking, putting on a coat, making coffee, preparing lunch, eating, taking off their shoes, reading a newspaper, drinking coffee and washing hands. The order of the activities was randomized between subjects by a dedicated computer program. Subjects were allowed to carry out the activities in their own way and at their own pace. They were free to take a rest between activities at any time.

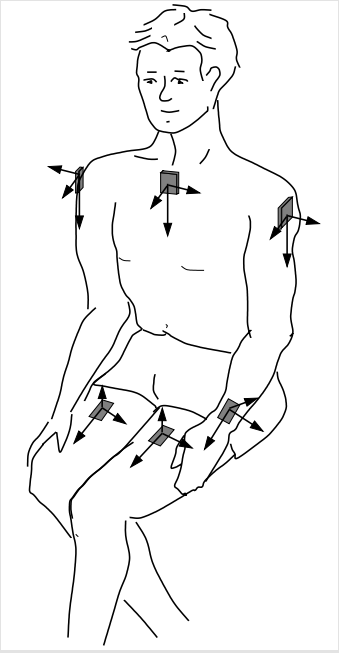

Figure 3.1. Schematic overview of the position of accelerometers on the body. The directions for measurement of acceleration by each set of accelerometers are indicated by arrows.

Data acquisition

The movements and postures were automatically measured using accelerometers and a portable data recorder. Six sets of 3 orthogonal accelerometers (ADXL-202, Analog Devices, USA) were used, which were placed at six different positions of the body. These 6 positions were at both upper arms (just below the shoulder), both upper legs (halfway the upper leg), at the wrist of the most dyskinetic side and at the trunk (top of the sternum; see

Figure 3.1). The accelerometer signals were digitally stored on a recorder (Vitaport 3, TEMEC instruments, Kerkrade, The Netherlands) that was attached to a belt around the patient's waist. The accelerometer signals were sampled at a frequency of 256 Hz, low-pass filtered using a moving averaging window and stored at a sample frequency of 64 Hz. Advantages of this procedure are that it does not require a neurologist and that it can easily be placed within 15 minutes.

Thus far, the most reliable method to assess the severity of LID in daily life is to have the performance rated by experienced physicians. Therefore, the behavior of the patients was videotaped. The videotapes were used to rate the severity of LID on the modified AIMS scale (m-AIMS; Guy, 1976) off-line by two experienced physicians, independently. The m-AIMS rating scale is a five-point scale with a value between 0 (absence of dyskinesia) and 4 (extreme dyskinesia) (Guy, 1976). Rating was done for each of the four limbs and for the trunk, separately. Data in a hypokinetic *off*-period without LID was excluded from further analysis.

Each start and end of an activity was stored on the data recorder using a radiographic system. A receiver was connected to the data recorder and a sender was attached to a portable computer. When the patient started an activity, the experimenter pressed a key on the portable computer indicating the task that was started. The computer immediately transmitted a code to the receiver and the code was written on a separate channel of the data recorder worn by the patient. Simultaneously with recording onset and offset, an LED attached to the receiver was switched on and off. This switching LED informed the physicians to start or to end the video rating of LID.

Because different tasks had a different duration and because the severity of LID could fluctuate during an activity, we divided each task in subsequent time intervals of 1 minute, because a time resolution of 1 minute is clinically relevant and sufficient. Each 1-minute interval was evaluated separately, i.e. the severity of LID was video-rated by the physicians and the accelerometer characteristics were calculated for all subsequent 1-minute intervals.

Data Analysis

For each one-minute interval signal, several variables were calculated from the accelerometer signals (to be described in detail later) before being presented to the neural network. The neural network was trained with these variables as input and the rating scores given by the physicians as output. First, the preprocessing of the 1-minute accelerometer signals will be described, followed by the training and classification procedure with the neural network.

Preprocessing accelerometer signals

Each raw accelerometer signal was filtered by a second-order low-pass digital Butterworth filter with a 3-dB cut-off frequency of 8Hz. Accelerometers measure a contribution of gravity related to the orientation of the accelerometer and a contribution related to linear acceleration of the accelerometer. These components cannot be distinguished from each other. However, when there is movement both components will change; thus, any change in the accelerometer signal will reflect movement of the accelerometer. For this reason, the derivative of the accelerometer signal was used as a measure of the amount of movement made by the subject. At each of the six body segments, we attached three accelerometers orthogonal to each other. To calculate the frequency and amplitude of body segment movements, we took the square root of the sum of squares of the derivatives of the three accelerometer signals from that body segment. The result will be referred to as "segment velocity".

Table 3.1. Input variables and their description

Symbol	Description
$\overline{V}$ *segment*	Mean segment velocity
$\overline{V}_{<3Hz}$ *segment*	The mean segment velocity for frequencies below 3Hz
$\overline{V}_{>3Hz}$ *segment*	The mean segment velocity for frequencies above 3Hz
$\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *segment*	The ratio between $\overline{V}_{<3Hz} segment$ and $\overline{V}_{>3Hz} segment$
SD(*V*) *segment*	The standard deviation of the segment velocity
$\%V_{\theta}$ *segment*	Percentage of time that a segment was moving. A segment was considered as moving when the low-pass filtered segment velocity was above a threshold of about 0.05m/s.
$\overline{V}_{\theta}$ *segment*	The mean segment velocity when the segment was considered to be moving, i.e. when $Vsegment > V_{\theta} segment$
P_{1-3Hz} *segment*	Power for frequencies in the range between 1 and 3Hz
$P_{>3Hz}$ *segment*	Power for frequencies above 3Hz
$\overline{\rho}_{segment-segment}$	The mean value of the normalized cross-correlation between the segment velocities of different segments.
$\max(\rho_{segment-segment})$	The maximum value of the normalized cross-correlation between the segment velocities of different segments.
%*sitting*	The percentage of time that a patient was sitting
%*upright*	The percentage of time that a patients body was upright

Definition of the input variables to the neural network. The variables were calculated for each one-minute interval. The segment could be the most dyskinetic leg (mleg), the less dyskinetic leg (lleg), the most dyskinetic arm (marm), the less dyskinetic arm (larm) and the trunk (trunk). For detailed explanation of the variables, see text.

For each of the body segments, the segment velocity was used to compute various variables for each 1-minute interval. The variables and their descriptions are shown in Table 3.1 and were calculated by a dedicated computer program. The first nine variables were calculated for each of the six different body segments. The variables $\overline{V}$ *segment*, $SD(V)$ *segment*, $\%V_\theta$ *segment* and $\overline{V}_\theta$ *segment* represent the mean velocity of a segment, the standard deviation relative to the mean velocity, the percentage of time a segment is moving, and the mean velocity when a segment moves, respectively. The variables $\overline{V}_{<3Hz}$ *segment*, $\overline{V}_{>3Hz}$ *segment*, $\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *segment* represent the mean segment velocity for frequencies below and above 3 Hz, and their ratio, respectively, These variables were used because it has been shown before that dyskinesia becomes manifest in the higher frequency domain (Hoff et al., 2001a; Manson et al., 2000a). Because the signal power for frequencies in the range between 1 and 3 Hz (P_{1-3Hz} *segment*) and above 3Hz ($P_{>3Hz}$ *segment*) gave a good performance in classifying the severity of LID in the study of Manson and colleagues (2000a), these accelerometer characteristics were also calculated. The cross-correlation between accelerometer signals from different body segments gives an indication of the coordination of movements of these segments. A high correlation (near one) indicates that movements of the two limb segments always covary, whereas a value near zero indicates that movements of the two limbs are uncorrelated. For this study, we calculated the mean cross-correlation between the velocity of two segments ($\overline{\rho}_{segment-segment}$) and the maximum of the cross-correlation ($\max(\rho_{segment-segment})$). The percentage of the time a patient was sitting ($\%sitting$) and/or when the patient was standing or walking (%*upright*) were also used as variables. These variables were calculated using the accelerometer signals of the trunk and the leg in a similar way as in Veltink and coworkers (1996). The first nine variables were calculated for each of the six segments, which gave 54 different variables. Other variables were the mean value of the auto- and cross-correlation (n = 21) and the maximum value of the cross-correlation between movements of the six body segments gave another 36 variables. These variables, together with the percentage of time while the patient is sitting or while the patient's body was upright added another 2 variables, which brings the total number of variables to 92. All these variables were presented as input variables for the neural network.

Neural network

The neural network used in this study was a MultiLayer Perceptron (MLP) with an input layer, one hidden layer and an output layer. Each layer has several units and each unit is connected to all units in the next layer. As input variables, we used the variables derived from the accelerometer signals (see Table 3.1). The number of units in the hidden layer is crucial for the ability of the network to generalize, which is the ability to give a proper classification for a new input pattern, which the network has not encountered before. There

was one output unit for each body segment, the value of which reflects the severity of LID of that body segment. This segment could be the most dyskinetic arm, the trunk, or the most dyskinetic leg. The output of the units in the hidden layer was given by a hyperbolic tangent sigmoid transfer function that gives a value between –1 and +1. The output of the unit in the output layer was given by a linear transfer function and had a value in the range between 0 and 4 reflecting the AIMS score. Neural networks need a set of data, which provide examples how sets of input values are related to the output (training-set). The neural network uses these examples to adjust the weights between units in subsequent layers in order to minimize the error between the desired network output and the neural network output for each example. This is called a training process. After training, the network was tested using data, which were not used during the training process (test-set). The neural network was trained using backpropagation. (For a review of neural networks, see Herz et al. (1991))

Evaluating the neural network

The performance of the network was evaluated using the mean square error (MSE) between the neural network output and the score given by the physicians. Because physicians could disagree in their rating, the mean value of the scores of the two physicians was used for training and testing the neural network. The physicians never had a difference in score larger than 1. In addition, the percentage of correctly classified signals by the neural network was used as a second criterion to evaluate the performance of the network. Because physicians rate dyskinesia by integers in the range between zero and four, the neural network classification was seen as correct when the difference between the neural network output and the score given by the physicians was smaller than 0.5. In other words, a classification was seen as correct when the rounded neural network output was exactly the same as that by the physicians.

The complexity of a network depends upon the number of units in the hidden layer and the number of variables used as input. A complex network will result in a good performance on a training set but can give a poor performance on a test-set as a result of overfitting of the data-set, i.e., the network has a poor generalization performance. For this reason, neural networks with various numbers of hidden units were trained to assess the severity of the most dyskinetic leg, the most dyskinetic arm, and the trunk. For each number of hidden units, the procedure of forward selection (Laar et al., 1999) was used to find the most valuable input variables to the neural network to assess the severity of LID. Forward selection means that we started with an empty variable set, and add, one after another, the variable that causes the largest reduction of the MSE between the neural network output and the score given by the physicians. After each step, we look for the next most important variable, and so forth. This procedure provides insight into the variables that are used by the neural network and that characterize its performance.

The generalization performance of the network was tested by training the network with 80% of the data set and testing the network with the remaining 20% of the data. This procedure was done 50 times for different randomly selected sets of training and test sets. The optimal architecture of the network was seen as the network, which gave on average the smallest mean square error (MSE) on the test set for the 50 randomly selected sets.

The first goal of the study was to test the possibility to detect and assess the severity of LID for patients with Parkinson's disease by studying a large variety of daily life activities, i.e., the network's ability to generalize over various tasks. However, the network should also be able to classify the severity of LID for new patients, which the network has never seen before, i.e., the network should also be able to generalize over patients. The network architectures with the best performance in detecting and assessing the severity of LID in a large variety of daily life activities were used to test the performance for new patients. For this testing, the neural network was trained with all data except for the data of one patient ("leave-one patient-out"). The data of the remaining patient was predicted using the trained neural network. This "leave-one-out" method was applied for each patient and gave a good impression of the ability of the network to classify the severity of LID for patients, which the network has not seen before. The performance of the network was evaluated using two measures: the mean square error between the neural network output and the score given by the physicians, and the percentage of correctly classified data.

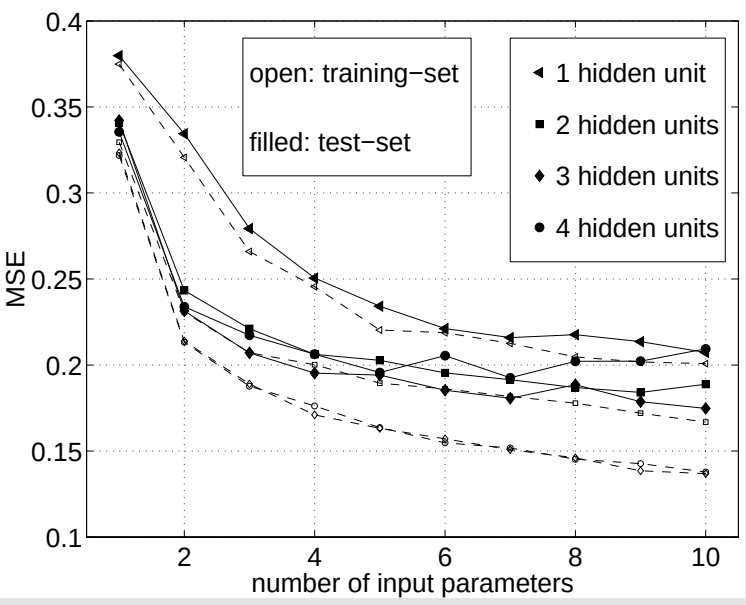

Figure 3.2. The mean square error on the training set (open symbols and dashed lines) and test set (filled symbols and solid lines) for neural networks with 1, 2, 3, and 4 units in the hidden layer. Each network was trained with data for the most affected leg using the input parameters (See *Patients and Methods* and Table 3.1) and the rating by the physician.

Results

Figure 3.2 shows the MSE for the training set (open symbols and dashed lines) and

test-set (filled symbols and solid lines) for neural network architectures with various numbers of units in the hidden layer. The MSE is plotted as a function of the number of input variables for the most dyskinetic leg ordered according to their relevance for the detection and assessment of LID. As shown in Figure 3.2, the MSE starts to decrease when the number of input variables increases for each number of hidden units. When the number of input variables becomes larger than four, the MSE for the training set decreases only slightly. The MSE on the test set shows initially a decrease for each added variable, followed by an increase in MSE when the number of input variables becomes larger. The increase in MSE on the test-set for large numbers of input variables is the result of overfitting of the data.

The network with three hidden units and seven input variables as input gave the best performance on the test set (smallest MSE) for the most dyskinetic leg (see Figure 3.2). For the arm, a network with two hidden units and six variables as input gave the smallest MSE on the test set. For the trunk, the best performance was obtained for a network with only one hidden unit. The optimal number of input variables appeared to be relatively large (n = 12) Table 3.2 shows a list of the relevant input variables, which result from the neural network and the forward selection procedure, in order of importance for each of the three segments..

Table 3.2. Relevant input parameters

Stage	Arm	Trunk	Leg
1	$\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg*	$\%V_\theta$ *trunk*	$SD(V)$ *lleg*
2	$\overline{\rho}_{wrist-trunk}$	$SD(V)$ *lleg*	$\%V_\theta$ *mleg*
3	$\%V_\theta$ *mleg*	$\overline{V}_{<3Hz}$ *Trunk*	%*sitting*
4	$\%V_\theta$ *wrist*	$\%V_\theta$ *lleg*	$\overline{\rho}_{lleg-trunk}$
5	$\overline{\rho}_{wrist-larm}$	$P_{>3Hz}$ *marm*	P_{1-3Hz} *trunk*
6	%*sitting*	P_{1-3Hz} *mleg*	$\overline{V}_\theta$ *mleg*
7	-	$\overline{\rho}_{mleg-trunk}$	$\max(\rho_{mleg-trunk})$
8	-	$P_{>3Hz}$ *mleg*	-
9	-	P_{1-3Hz} *lleg*	-
10	-	$\overline{V}_{>3Hz}$ *marm*	-
11	-	$\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *larm*	-
12	-	$SD(V)$ *wrist*	-

Input variables, relevant for the detection and classification of LID for the arm, trunk and leg, in order of importance. The order of importance was determined using forward selection for the network with the smallest mean square error (MSE) between neural network output and the score given by the physicians on the test set for the arm (2 hidden units), the trunk (1 hidden unit), and the leg (3 hidden units). Subscripts refer to marm (most dyskinetic arm); larm (less dyskinetic arm); mleg (most dyskinetic leg) and lleg (less dyskinetic leg).

A variety of variables are important and the important variables differ for different body segments. For the arm and especially for the trunk, variables related to movements of other body segments appeared to be relevant. For the leg, variables of both legs and the trunk and the cross-correlation between these segments appeared to be relevant

The MSE and the percentage of correctly classified data on the training and test set for the best performing networks on the test set for 1-minute intervals are shown in Table 3.3. The results in Table 3.3 indicate that, in general, the error between the score by the physicians and by the neural network (0.19 or less) is small relative to the AIMS scale, which ranges between 0 and 4 with integer increments. The percentage of correctly classified 1-minute intervals on the test set has the largest value for the trunk (83.0±4.0%) and was slightly smaller for the arm (77.0±3.1%) and the leg (76.9±3.9%). The correlation coefficients between the neural network output on the test set and the physicians rating were 0.71, 0.87 and 0.80 for the arm, trunk, and leg, respectively.

Table 3.3 Data from the best performing networks

Segment	**MSE (one-minute interval)**		**%good (one-minute interval)**		**%good**
	Training-set	Test-set	Training-set	Test-set	**(15min.)**
Arm	0.17±0.01	0.19±0.02	78.3±0.9	77.0±3.1	**93.7**
Trunk	0.14±0.01	0.14±0.02	83.4±0.9	83.0±3.4	**99.7**
Leg	0.15±0.01	0.18±0.03	80.5±1.4	76.9±3.9	**97.0**

Performance of the neural network averaged over all 1-minute time intervals of the 2.5 hours session (columns 2, 3, 4, and 5) and the percentage of correctly classified data in 15-minute time interval (column 6). Performance of the neural network is expressed by the mean and standard deviation of the mean square error (MSE) between the neural network output and the score given by the physicians (columns 2 and 3) and by the percentage of correctly classified activities (%good) (columns 4, 5 and 6) for the arm, trunk, and leg.

Figure 3.3 shows an example of the scores given by the physician and the scores given by the neural network on a test set for 81 one-minute intervals. These 81 one-minute intervals were taken out of the 2.5 hours session of a patient in which periods of rest were not shown in order to present the performance for a representative set of activities. The scores predicted by the neural network do agree well with the scores given by the physicians. Both scores change almost simultaneously in time over the time interval of 81 minutes. For scores for which the physicians disagree (in these cases the average of the physician's score was 0.5, 1.5 or 2.5), the network gave a value between the scores given by the physicians. In general, the difference in rating given by the physicians and the network is

0.5 or smaller. Because the patient showed only mild symptoms of dyskinesia, Figure 3.3 shows that the neural network was sensitive and accurate in detecting LID.

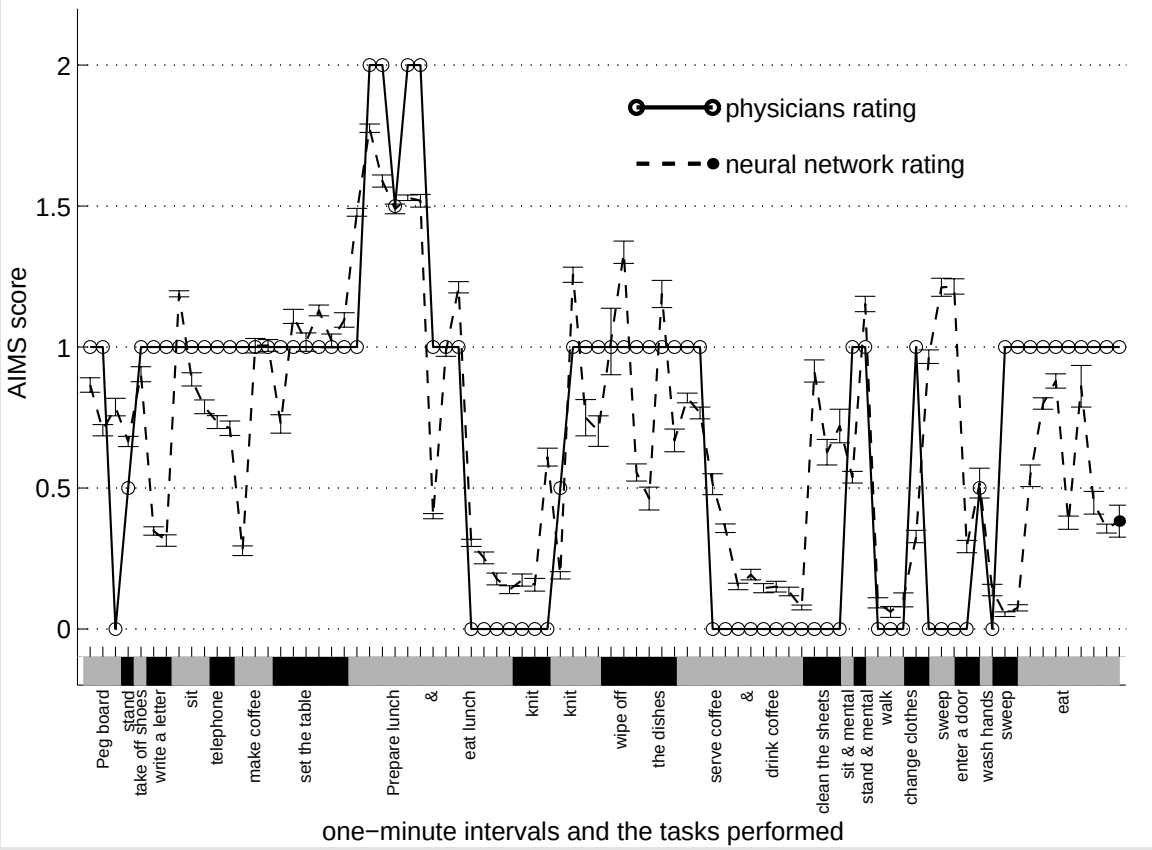

Figure 3.3. Example of the AIMS rating given by the physicians (circles) and predicted by the neural network (dots with error bars) for the trunk for eighty-one one-minute intervals of various activities.

The neural network classification was considered to be correct when the difference between the neural network output and the score given by the physicians was smaller than 0.5. It would be interesting to see what the percentage of correctly classified data would be for other error margins between the neural network output and the physician's score. Figure 3.4 shows the percentage of correctly classified 1-minute intervals on the test set as a function of the error margin for the arm, leg, and trunk for the whole population of data. More than 95% of the 1-minute intervals had a difference less than 0.85 between neural network output and the score given by the physicians. When differences up to 1.0 were allowed, more than 98.0% of the 1-minute intervals were classified correctly. This finding suggests that, if the rating by the neural network were different from the physician's rating, it was in the grade next to the score given by the physicians.

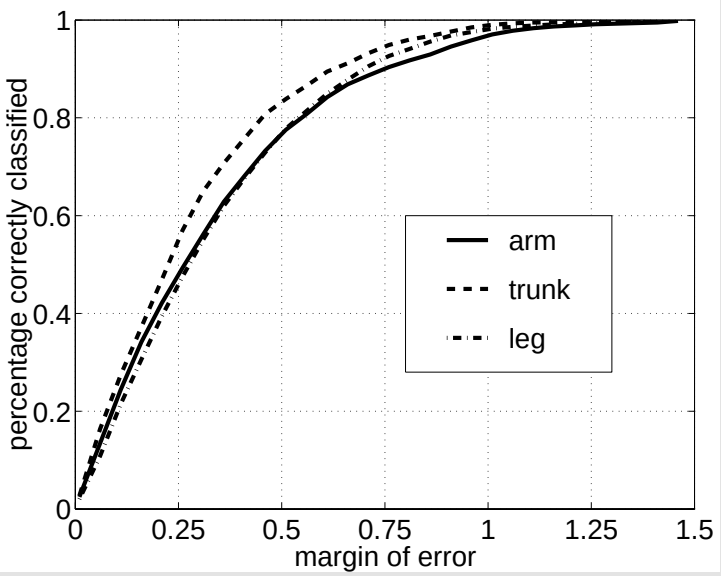

Figure 3.4. Percentage of correctly classified data in the test set as a function of the error margin for the arm (solid line), trunk (dashed lines) and leg (dashed-dotted line).

From a clinical point of view, physicians are mainly interested in whether patients suffer from dyskinesia for at least a few minutes. Therefore, we determined the performance of the network under the constraint that it should correctly predict dyskinesia or the absence of dyskinesia for longer periods. For periods of 15 minutes, the neural network correctly classified dyskinesia or absence of dyskinesia in 93.7, 99.7, and 97.0 percent for the arm, trunk, and leg respectively (see Table 3.3).

Recently, Manson et al. (2000a) reported a good Spearman rank correlation between acceleration signals in the 1 to 3 Hz frequency band and the rating on the modified AIMS scale. For the data in our study, the Spearman rank correlation between the acceleration in the 1 to 3 Hz frequency (P_{1-3Hz} *segment*) and the m-AIMS score for the arm, trunk, and leg was 0.18, 0.30, and 0.21, respectively. As shown in Table 3.2, the neural network indicated other variables with more predictive power in addition to the acceleration in the 1 to 3 Hz frequency band. The most valuable variables, the ratio between low and high frequencies of the most affected leg, the percentage of the time that the trunk was moving, and the standard deviation of the leg (see Table 3.2), gave a Spearman rank correlation of 0.38, 0.44 and 0.37 for the arm, trunk, and leg, respectively. This finding means that these most valuable variables contribute approximately 2 to 4 times more in explaining the AIMS score than the acceleration in the 1 to 3 Hz frequency range for the data in our study.

To demonstrate the neural network‘s ability to distinguish LID from voluntary movements, the performance of the network was evaluated for 3 different groups of activities. The first group included the activities sitting and standing with or without a mental task. During these activities, patients were ordered to abstain from any voluntary movement and not to suppress any involuntary movements. The second group consisted of activities for

which patients now and then made voluntary movements. This second group included activities such as drinking coffee, reading a newspaper, making a phone call, and writing. The third group consisted of activities for which patients made voluntary movements for almost the entire period such as making coffee, walking, setting the table, dressing, etc. The performance of the neural network output was considered to be correct when the neural network gave a value smaller than 0.5 for the 1-minute intervals, which were rated by the physicians with the score 'zero' (no dyskinesia group), and when the network gave a score larger than 0.5 for the one-minute intervals, which were rated by the physicians with a rating 1 or higher (dyskinesia group). The percentage of correctly classified minutes for the different groups is shown in Table 3.4. The correct performance of the neural network is between 75% and 100%, depending on the type of movements. The best performance is obtained in the absence of voluntary movements and in the absence of dyskinesia. The network displayed some tendency to erroneously detect absence of dyskinesia in patients with mild dyskinesia who were trying to abstain from any voluntary movements. This is primarily because normal subjects, when sitting in a relaxed position, make small movements with the legs and arms, which are hard to distinguish from mild dyskinesia. In general, the neural network was able to correctly distinguish the large majority of LID movements from voluntary movements.

Table 3.4 Correctly classified minutes

	Segment	No Voluntary movements	Now-and-then voluntary movements	Many Voluntary movements
Absence of dyskinesia (aims=0)	Arm	100.0	79.6	78.5
	Trunk	100.0	98.5	88.3
	Leg	92.6	80.2	77.2
Dyskinesia (aims>=1)	Arm	75.0	90.0	79.4
	Trunk	94.6	84.7	90.4
	Leg	76.9	87.3	82.6

Percentage of correctly classified one-minute intervals with dyskinesia and absence of dyskinesia for time intervals without voluntary movement, intervals with activities requiring voluntary movements some now and then, and for intervals with activities which require frequent voluntary movements.

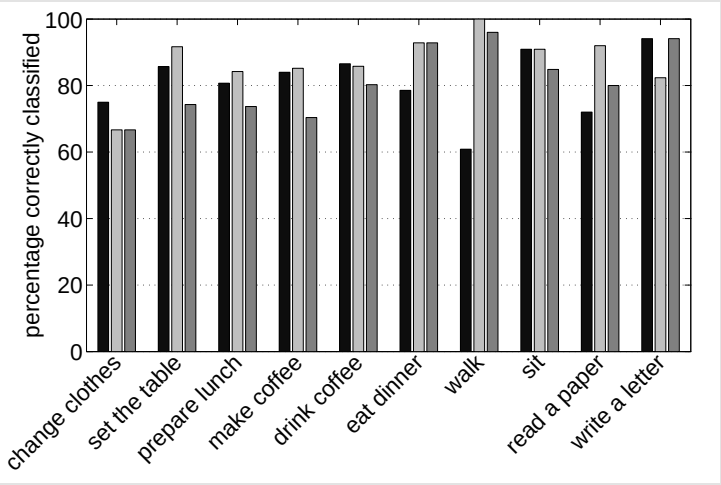

Figure 3.5. Percentage of correctly classified data for various activities. First bar is for the arm, second bar is for the trunk and the third bar is for the leg.

A more detailed overview of the rating performance by the neural network for various types of behavior with voluntary movements is shown in Figure 3.5, which shows the percentage of correctly classified behavior for a selection of activities. In general approximately 80% of the 1-minute intervals of each activity was correctly classified. Classification algorithms in previous studies showed discrepancies with the rating by physicians for activities with voluntary movements and especially for walking (Hoff et al., 2001a; Keijsers et al., 2000; Manson et al., 2000a). The neural network gave an extremely well-fit classification for 1-minute intervals of walking for the trunk (100%) and the leg (96%), but less so for the arm (61%).

Table 3.5. Data from the network for 'leave one patient out'

	MSE (one-minute interval)		**%good (1-minute interval)**		**%good**
Segment	Training-set	Test-set	Training-set	Test-set	**(15 min)**
Arm	0.17±0.01	0.22±0.10	78.4±1.1	74.0±11.8	93.6±15.1
Trunk	0.14±0.01	0.15±0.11	83.3±0.9	82.4±16.5	99.5±1.7
Leg	0.15±0.00	0.20±0.08	81.2±0.8	70.3±14.7	92.7±11.1

Performance of the neural network over different patients using the leave-one-output method. Performance of the neural network (mean square error (MSE) and the percentage correctly classified activities by the neural network (%good) for one-minute intervals (columns 2,3,4 and 5). The percentage of correctly classified data for 15-minute time interval data (column 6).

To test the ability of the network to classify the severity of LID for patients that the network has not seen before, neural networks were trained with all data except for the data of 1 patient. Thereafter, the trained network was used to predict the severity of LID for the

remaining patient. The mean and standard deviation of the MSE and the percentage of correctly classified 1-minute intervals for the various subjects for the arm, trunk, and leg are shown in Table 3.5. The performance of the network for data in a 15-minute interval is also shown in Table 3.5 (see column 6). The performance of the networks is approximately the same as that shown in Table 3.3, indicating that the neural network could equally well generalize over activities and subjects.

Discussion

Recent studies have indicated the validity of ambulatory accelerometry in assessing the severity of LID (Burkhard et al., 1999; Hoff et al., 2001a; Keijsers et al., 2000; Manson et al., 2000a). However, previous studies have not been adequately sensitive, nor can they distinguish between voluntary movements and LID. Another important limitation of studies to date has been the small number of tasks involved, and the fact that they have been performed in a laboratory setting. In the present study, patients performed a large variety of daily life activities in a natural environment for a long duration. The neural network was able to detect and assess the severity of LID correctly for a large fraction of tasks. When the rating by the neural network differed from the rating given by the physicians, the difference in rating was small, and in the worst cases the rating was in the grade next to that indicated by the physicians.

Previous studies (Burkhard et al., 1999; Hoff et al., 2001a; Manson et al., 2000a) have used linear classification techniques to detect and to assess LID. In our previous study (Keijsers et al., 2000), the best performing neural network did have one hidden unit, which is equivalent to a linear classification. With the larger and richer data set in this study we found that the optimal number of hidden units for the neural network for rating LID is three for the leg and two for the arm. This finding indicates that nonlinear interactions between various movement variables (which may not have been obvious in our previous study due to the limited number [n = 7] of tasks) are important for the proper rating of LID. For the trunk the best performing neural network had only one unit in the hidden layer, indicating that a linear technique may be sufficient. However, in this case, the number of input variables, which contribute information to the detection and classification of LID, appeared to be relatively large (n = 12).

In our comparison of rating by physicians and by the neural network, we have used the averaged rating by the physicians. Assuming that experienced physicians rate LID in the same class or in neighboring classes, we considered the rating by the neural network incorrect when the rating by the neural network differed by more than 0.5 from the average of the rating by the physicians. With that criterion, approximately 80% of the 1-minute intervals

were classified correctly (see Table 3.3 and 3.5). However, the criterion of 0.5 may be somewhat arbitrary. The physician's rating is semi-quantitative and not sensitive to small changes. Moreover, the rating by the physicians will presumably be affected by ratings in previous minutes. In many cases, we observed that the changes in the rating by the neural network anticipated those by the physicians. These influences on the physician's rating triggered us to consider the score for other error margins. When the error margin was extended to 1.0, the correct score went up to more than 98.0%. Irrespective of the question which error margin to use, our results demonstrate that any differences between the rating by the physicians and the neural network do not differ by more than one grade on the AIMS scale.

Another aspect of the rating by the neural network was that any difference with the rating by the physicians usually lasted for one minute only. When periods with a longer duration where evaluated, the error rate decreased and the correct performance increased to 93.7, 99.7, and 97.0 % for the arm, trunk, and leg, respectively. These results indicate that the procedure described in this paper to detect and assess LID seems a valid method for practical use.

A major advantage of using neural networks for the detection and rating of LID with the forward selection procedure to find the most relevant variables is that this procedure searches for the most valuable variables without any prior information and restriction. In general, the percentage of time that a segment was moving ($\%V_{\theta}$ *segment*), the cross-correlation between segments ($\overline{\rho}_{segment-segment}$), and variables evaluating the signals in the frequency domain appeared to be the most important variables. These variables are in line with the most important variables found in a previous studies (Hoff et al., 2001a; Keijsers et al., 2000; Manson et al., 2000a).

One of the most important variables appeared to be the percentage of time that the arm, trunk, or leg was moving. The importance of this variable is obvious, because a small percentage indicates few movements and probably no dyskinesia, whereas a large percentage indicates many movements and, thus, a possibility that the subject might suffer from dyskinesia.

One of the main difficulties in assessing LID is the ability to distinguish LID from voluntary movements. Hoff et al. (2001a) and Manson et al. (2000a) reported that acceleration signals in the 1 to 3 Hz frequency band correlated well with the modified AIMS scale and stated that dyskinesias occur in a higher frequency domain than voluntary movements. In our analysis, the acceleration signals in the range between 1 and 3 Hz also appeared to be a variable, which contributes to the detection and rating of LID. However, the power of the acceleration signals in the 1 to 3 Hz frequency domain explained only a small fraction of the severity of LID. This finding indicates that the frequency range of accelerometer signals of voluntary movements is not disjunct from that of the accelerometer

signals for dyskinesias which is in agreement with previous reports (Hoff et al. 2001a; Redmond and Hegge, 1985).

Moreover, the neural network analysis revealed several other variables which can contribute to distinguish LID from voluntary movements, such as the cross-correlation between acceleration signals from two different limb segments and by comparing the movements of various limb segments. This can be understood from the fact that dyskinesia is frequently observed in multiple body segments (Marconi et al., 1994). In our study, this resulted in a small value of the correlation between movements of these body segments combined with high values for the percentage of time of moving for these body segments. We also observed that patients suffering from mild dyskinesias showed dyskinesia only in a single limb or in the trunk. In such case the correlation coefficient was zero if one of the body segments did not move. In case of dyskinesia superimposed on voluntary movements, such as in walking, the correlation between movements of the arm and leg does not provide much information. In that case, the power in the frequency range below and above 3 Hz was used to detect dyskinesia, in agreement with the results of previous studies. A detailed description of the contribution of various parameters requires more sophisticated analyses, which is outside the scope of this paper.

Our results showed that the neural network was able to distinguish LID from voluntary movements (see Table 3.4). The performance of the neural network was slightly less for the group of patients with dyskinesia, who abstain from voluntary movements, and for the group of patients without dyskinesia, who made many voluntary movements. For the group of patients with dyskinesia who abstained from voluntary movements, the neural network had some difficulty to distinguish mild dyskinesia from normal small movements of the arm and the leg, which occur now and then when subjects sit relaxed for some time. In normal daily life, patients hardly ever abstain completely from any voluntary movements. Therefore, the second group of tasks, wherein patients occasionally made voluntary movements, may be more illustrative for daily life situations with few voluntary movements. For this second group of tasks, the neural network showed a good performance in detecting dyskinesia.

The network rated some voluntary movements as dyskinesia for patients with absence of dyskinesia who made many voluntary movements. This misclassification is most frequently observed in activities such as washing the dishes or sweeping the floor. These typical activities show voluntary movements that contain movement characteristics similar to that of dyskinesia.

The obvious question to ask is: what explains the better performance of rating in this study relative to that in previous studies? A possible explanation is that previous studies used a limited set of tasks, which had to be performed in a highly controlled laboratory setting (Burkhard et al., 1999; Hoff et al., 2001a; Keijsers et al., 2000; Manson et al., 2000a). This strategy may have resulted a limited data set with possibly some unnatural behavior of

the patients. The present study tested patients with varying degrees of severity of LID in a large variety of daily activities. This larger number of activities and varying degree of severity of LID provides more information for the adaptive neural networks to find the proper variables to distinguish between voluntary movements and LID. These variables and their mutual linear and nonlinear connections are probably not disclosed with the methods used by other investigators. The next step will be to investigate how the neural network combined the various variables for rating. This will provide more information about the characteristics of LID in comparison to that of voluntary movements.

In conclusion, our method accurately assessed the severity of LID and distinguished LID from voluntary movements in a daily life situation. The difference between the neural network output and the score by the physicians was small and, worst case, the rating by neural networks was in the class next to that indicated by the physician. Therefore, the method used in this study could be operating successfully in unsupervised ambulatory conditions.

Movement parameters that distinguish between voluntary movements and levodopa induced dyskinesia in Parkinson's disease

Adapted from: Keijsers NLW, Horstink MWIM, Gielen CCAM. Hum Mov Sci 22: 67-89, 2003; .

Introduction

After several years of levodopa medication, many patients with Parkinson's disease suffer from levodopa induced dyskinesia (LID) (Nutt, 1990; Horstink et al., 1990b; Marsden, 1994; Nutt et al., 1995). To alleviate or reduce these dyskinesias, several pharmacological and surgical treatments have been introduced (Brotchie, 1998; Manson et al., 2000b; Fraix et al., 2000; Lang, 2000; Rascol, 2000b). The benefits of these interventions have been evaluated using self-report by the patient or by using semi-quantitative rating scales during consults (Goetz, 1999; Damier et al., 1999; Widner & Defer, 1999). However, self-assessment can be unreliable and motor behavior of patients during a consult is not always representative for the behavior in daily life (Golbe & Pae, 1988; Goetz et al., 1997; Vitale et al., 2001). For these reasons, an ambulatory assessment of LID would be highly useful (Brown & Manson, 1999).

Recently, several investigators successfully used an ambulatory accelerometry to monitor (abnormal) activities of patients (Veltink et al., 1996; Busmann et al., 1998a,b; Dunnewold et al., 1998). Accelerometry was also used for assessing the severity of dyskinesia in several other studies (Burkhard et al., 1999; Keijsers et al., 2000; Manson et al., 2000a; Hoff et al., 2001a; Keijsers et al., 2003). The main challenge in automatically assessing LID is to distinguish between dyskinesias and voluntary movements. This requires information about the specific movement features, which distinguish voluntary movements from dyskinesias. Most studies focused mainly on the frequency and/or amplitude of the accelerometer signals to detect LID and to assess the severity of LID (Burkhard et al., 1999; Manson et al., 2000a; Hoff et al., 2001a). However, some studies reported that there is a large overlap in the frequency range of voluntary movements and dyskinesias (Keijsers et al., 2000; Hoff et al., 2001a; Keijsers et al., 2003), which suggests that frequency components alone will not be able to provide a complete distinction between LID and voluntary movements. This may explain why Hoff et al. (2001a) were successful to detect dyskinesia when subjects abstained from any voluntary movements, but could not successfully assess the severity of LID for patients who made voluntary movements. In the study of Manson et al. (2000a), the authors did succeed to distinguish between LID and voluntary movements by using the accelerations in the 1-3 Hz frequency domain. However, all patients in the study of Manson et al. (2000a) suffered from severe dyskinesias and it is not clear whether the same analysis would also be successful to detect mild dyskinesias. Another explanation for the different results in the studies by Hoff et al. (2001a) and by Manson et al. (2000a) might be related to the fact that these studies tested patients in different sets of tasks and that the set of tasks (like in most other studies, Keijsers et al., 2000) was a very limited set of daily life activities in a laboratory setting.

To study the effect of task conditions in a group of patients with varying degrees of

dyskinesia, Keijsers et al. (2003) monitored patients while performing a large variety of daily life tasks in a natural environment for a long period of time. In that study, a neural network was used to analyze the data and to assess the severity of LID. The neural network was highly successful in detecting and assessing the severity of dyskinesia and revealed considerable improvement upon that of previous studies. The neural network correctly classified dyskinesia or the absence of dyskinesia in 15-min intervals in 93.7%, 99.7% and 97.0% of the time for the arm, trunk and leg, respectively.

The excellent performance of the neural network raises the question whether it would be possible to obtain insight in the various parameters, which allow the detection of LID and the distinction between LID and voluntary movements. This is important for two reasons. The first reason is that acceptance of a new technique will be easier if physicians, who will use the technique, do understand why it is successful. In our case, this requires that physicians will be able to match their own criteria for the detection and rating of dyskinesia with the criteria provided by the neural network. The other reason is that insight in the movement parameters, which underlie pathological behavior, might be valuable for understanding normal motor behavior. For example, several studies have shown that angular velocities in elbow and shoulder are highly correlated in normal aiming movements of the hand (Soechting et al., 1986; Gielen et al., 1997). This has been interpreted as evidence for the existence of specific muscle synergies in human motor control. It would be interesting to investigate whether and to what extent muscle synergies are also observed in LID.

In our previous study (Keijsers et al., 2003), we reported the performance of neural networks in detecting and assessing dyskinesia and the performance of neural networks to distinguish dyskinesia from voluntary movements. In this study, we will focus on the architecture of the trained neural network to extract the relevant parameters that are used by the neural networks for a proper detection and rating of dyskinesia. In summary, the purpose of this study was to analyze the behavior of the optimal neural networks in the detection and rating of dyskinesia and to describe the relevant movement parameters and their relation to the severity of LID.

Methods

Thirteen patients with Parkinson's disease (8 male and 5 female) with a mean age of 61 years (range between 48 and 71) participated in this study. They had experienced symptoms of Parkinson's disease for between 10 and 21 years (mean 15 years). The patients were on levodopa medication for about fifteen years and all patients suffered from LID. During the test, seven patients showed a severity of dyskinesia varying between absence of dyskinesia and mild dyskinesia (rating between 0 and 1 on the AIMS scale (Guy,

1976). The other six patients showed a severity of dyskinesia varying between absence of dyskinesia to moderate dyskinesia (rating between 0 and 3 on the AIMS scale). All patients gave informed consent. The study was approved by the Medical Ethical Committee of the University Medical Center of the University of Nijmegen.

The study started between noon and one o'clock. The patients were continuously monitored for a period of approximately 2.5 h. During this period, the patients took their regular medication at their usual time. However, when dyskinesia did not occur halfway through the testing period, extra levodopa was taken to induce dyskinesia. The registration took place in a natural home-like setting in the occupational therapy department of the University Medical Center. During the 2.5 h monitoring session, the patients performed about 35 functional daily-life activities, such as walking, putting on a coat, making coffee, preparing lunch, eating, taking off their shoes, reading a newspaper, drinking coffee, and washing hands. The order of the activities was randomized between subjects by a dedicated computer program. Subjects were allowed to carry out the activities in their own way and at their own pace. They were free to take a rest between activities at any time.

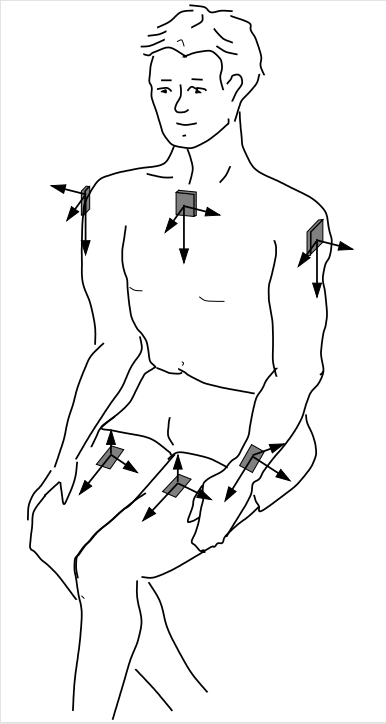

Figure 4.1. Schematic overview of the position of accelerometers on the body. The directions for measurement of acceleration by each set of accelerometers are indicated by arrows.

Data acquisition

The movements and postures were automatically measured using accelerometers and a portable data recorder. Six sets of three orthogonal accelerometers (ADXL-202, Analog Devices, USA) were used, which were placed at six different positions of the body.

These six positions were at both upper arms (just below the shoulder), at both upper legs (halfway between the hip and the knee), at the wrist of the most dyskinetic side, and at the trunk (top of the sternum) (see Figure 4.1). The accelerometer signals were digitally stored on a recorder (Vitaport 3, TEMEC instruments, Kerkrade, The Netherlands) that was attached to a belt around the patient's waist. The accelerometer signals were sampled at a frequency of 256 Hz, low-pass filtered using a moving averaging window over four samples and digitally stored at a sample frequency of 64 Hz.

Thus far, the most reliable method to assess the severity of LID in daily life is to have the performance rated by experienced physicians. Therefore, the behavior of the patients was videotaped. The videotapes were used to rate the severity of LID on the modified AIMS-scale (Guy, 1976) off-line by two experienced physicians, independently. A five-point scale was used for the rating with a value between 0 (no dyskinesia) and 4 (extreme dyskinesia). Rating was done for each of the four limbs and for the trunk, separately. Data in a hypokinetic *off*-period without LID was excluded from further analysis.

Each start and end of an activity was stored on the data recorder using a radiographic system. A receiver was connected to the data recorder, and a sender was attached to a portable computer. When the patient started an activity, the experimenter pressed a key on the portable computer indicating the task that was started. The computer immediately transmitted a code to the receiver and the code was written on a separate channel of the data recorder worn by the patient. Simultaneously with recording onset and offset, an LED attached to the receiver was switched on and off. This switching LED informed the physicians to start or to end the video rating of LID.

Because different tasks had a different duration and because the severity of LID could fluctuate during an activity, we divided each task in subsequent time intervals of 1 minute, because a time resolution of 1 minute is clinically relevant and sufficient. Each 1-minute interval was evaluated separately, i.e. the severity of LID was video rated by the physicians and the accelerometer characteristics were calculated for all subsequent 1-minute intervals.

Data Analysis

For each 1-minute interval signal, several variables were calculated from the accelerometer signals (to be described in detail later) before being presented to the neural network. The neural network was trained using these variables as input and the rating scores given by the physicians as output. Because the training of the neural network has been described in detail elsewhere (Keijsers et al., 2003), we will focus on the main aspects of the neural network architecture and training procedure.

Preprocessing accelerometer signals

Each raw accelerometer signal was filtered by a second-order low-pass digital Butterworth filter with a 3-dB cut-off frequency of 8 Hz. Accelerometers measure a contribution of gravity, related to the orientation of the accelerometer relative to gravity, and a contribution related to linear acceleration of the accelerometer. These components cannot be distinguished from each other. However, any movement will affect the sum of both components and thus any change in the accelerometer signal will reflect movement of the accelerometer. For this reason, the derivative of the accelerometer signal was used as a measure of the amount of movement made by the subject. At each of the six body segments we attached three accelerometers orthogonal to each other. This allows us to measure movement of body segments in all directions. To calculate the frequency and amplitude of body segment movements, we took the square root of the sum of squares of the derivatives of the three accelerometer signals from that body segment (see Eq. (1)). The result will be referred to as "segment velocity".

$$segment\ \ velocity\ = \sqrt{\sum_{i=1:3} (ds_i\ / dt)^2} \qquad (1)$$

where s_i refers to the signal from the i^{th} accelerometer.

For each of the body segments, the segment velocity was used to compute several input variables for a series of subsequent 1-minute intervals. The variables and their descriptions are shown in Table 4.1 and were calculated by a dedicated computer program. The first nine variables were calculated for each of the six different body segments. The variables $\overline{V}$ *segment*, $SD(V)$ *segment*, $\%V_\theta$ *segment* and $\overline{V}_\theta$ *segment* represent the mean velocity of a segment, the standard deviation relative to the mean velocity, the percentage of time a segment is moving, and the mean velocity when a segment moves, respectively. The variables $\overline{V}_{<3Hz}$ *segment*, $\overline{V}_{>3Hz}$ *segment*, $\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *segment* represent the mean segment velocity for frequencies below and above 3 Hz, and their ratio, respectively. These variables were used because it has been suggested before that dyskinesia differs from voluntary movements in the frequency content of the movements (Keijsers et al., 2000; Manson et al., 2000a; Hoff et al., 2001a). Based on the results from these studies, we took the signal power for frequencies in the range between 1 and 3Hz (P_{1-3Hz} *segment*) and above 3Hz ($P_{>3Hz}$ *segment*) as input parameters.

The cross-correlation between accelerometer signals from different body segments gives an indication of the covariation of movements of these segments. A high cross-correlation indicates that movements of the two limb segments covary, whereas a value near zero indicates that movements of the two limbs are uncorrelated. For this study, we calculated the mean normalized cross-correlation between the velocity of two segments ($\overline{\rho}_{segment-segment}$) and the maximum of the normalized cross-correlation

$(\max(\rho_{segment-segment}))$ defined as

$$\bar{\rho}_{segment\ 1-segment\ 2} = \frac{1}{T}\int_{0}^{T}\frac{1}{2T}\int_{-T}^{T} v_{s1}(t)v_{s2}(t-\tau)dt\,d\tau \quad (2)$$

$$\max(\rho_{segment\ 1-segment\ 2}) = \max(\frac{1}{2T}\int_{-T}^{T} v_{s1}(t)v_{s2}(t-\tau)dt) \quad (3)$$

, respectively, where v_{s1} and v_{s2} represent the segment velocity and T refers to the duration of the signals in time.

The percentage of the time a patient was sitting ($\%sitting$) and/or when the patient was standing or walking ($\%upright$) were also used as variables. These variables were calculated by using the accelerometer signals of the trunk and the leg in a similar way as done by Veltink et al. (1996).

Table 4.1. Definition of the input variables to the neural network

Symbol	Description
$\bar{V}$ *segment*	Mean segment velocity
$\bar{V}_{<3Hz}$ *segment*	The mean segment velocity for frequencies below 3Hz
$\bar{V}_{>3Hz}$ *segment*	The mean segment velocity for frequencies above 3Hz
$\bar{V}_{<3Hz}/\bar{V}_{>3Hz}$ *segment*	The ratio between $\bar{V}_{<3Hz}segment$ and $\bar{V}_{>3Hz}segment$
$SD(V)$ *segment*	The standard deviation of the segment velocity
$\%V_{\theta}$ *segment*	Percentage of time that a segment was moving. A segment was considered as moving when the low-pass filtered segment velocity was above a threshold of about 0.05m/s.
$\bar{V}_{\theta}$ *segment*	The mean segment velocity when the segment was considered to be moving, i.e. when $Vsegment > V_{\theta}segment$
P_{1-3Hz} *segment*	Power for frequencies in the range between 1 and 3Hz
$P_{>3Hz}$ *segment*	Power for frequencies above 3Hz
$\bar{\rho}_{segment-segment}$	The mean value of the normalized cross-correlation between the segment velocities of different segments.
$\max(\rho_{segment-segment})$	The maximum value of the normalized cross-correlation between the segment velocities of different segments.
$\%sitting$	The percentage of time that a patient was sitting
$\%upright$	The percentage of time that a patients body was upright

The variables were calculated for each one-minute interval. The segment could be the most dyskinetic leg (mleg), the less dyskinetic leg (lleg), the most dyskinetic arm (marm), the less dyskinetic arm (larm) and the trunk (trunk). For detailed explanation of the variables, see text.

The first nine variables were calculated for each of the six segments, which gave 54 different variables. Other variables were the mean value of the auto- and cross-correlations between movements of the six body segments (n = 21). The maximum value of the cross-correlation between movements of the six body segments gave another 36 variables. The percentage of time, while the patient is sitting or while the patient was standing or walking, added another two variables, which brings the total number of variables to 92. All these variables were presented as input variables for the neural network.

Neural network

The neural network used in this study was a MultiLayer Perceptron (MLP) with an input layer, one hidden layer, and an output layer. Each unit is connected to all units in the next layer. As input variables, we used the variables derived from the accelerometer signals (see Table 4.1). The number of units in the hidden layer is crucial for the ability of the network to generalize. Generalization is the ability to give a proper classification for a new input pattern, which the network has not encountered before. There was one output unit for each body segment, the value of which reflects the severity of LID of that body segment. This segment could be the most dyskinetic arm, the trunk, or the most dyskinetic leg. The output of the units in the hidden layer was given by a hyperbolic tangent sigmoid transfer function that gives a value between –1 and +1. The output of the unit in the output layer was given by a linear transfer function and had a value in the range between 0 and 4 reflecting the AIMS score. Neural networks need a set of data, which provide examples how sets of input values are related to the output (training-set). The neural network uses these examples to adjust the weights between units in subsequent layers in order to minimize the error between the desired network output and the neural network output for each example. Figure 4.2 shows a schematic overview of the data preprocessing and the subsequent neural network approach

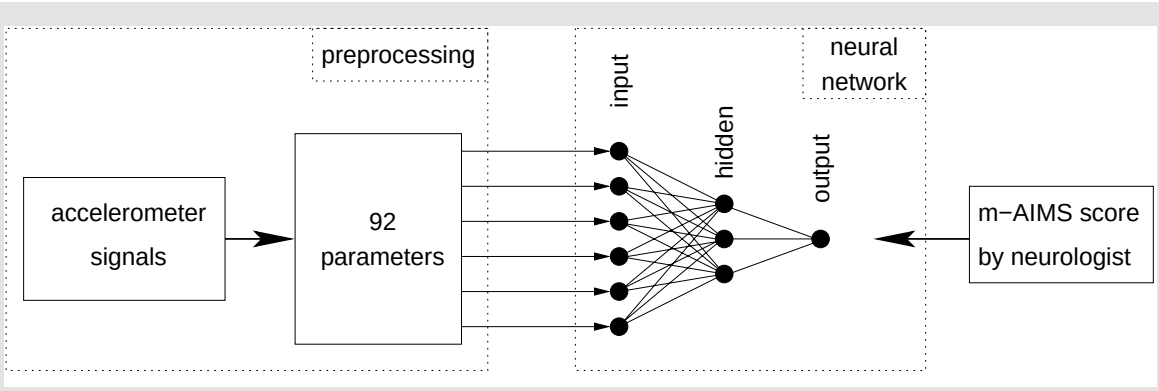

Figure 4.2. Schematic overview of the data preprocessing and the subsequent neural network approach in assessing the severity of dyskinesia. The neural network maps the parameters of the accelerometer signal (input) to the rating by the neurologist (output) by adjusting the connection between units in subsequent layers.

in assessing the severity of dyskinesia. The lower panel of Figure 4.2 shows a neural network with an input layer with six units, a hidden layer with three units and an output layer with one unit. After training, the network was tested using data, which had not been used in the training process (test-set). The neural network was trained using backpropagation. For a good review of neural networks, see Herz et al. (1991).

Evaluating the neural network

The performance of the network was evaluated using the mean square error (MSE) between the neural network output and the score given by the physicians. Because physicians could disagree in their rating, the mean value of the scores of the two physicians was used for training and testing the neural network. The physicians never had a difference in score larger than 1. In addition, the percentage of correctly classified signals by the neural network was used as a second criterion to evaluate the performance of the network. Because physicians rate dyskinesia by integers in the range between zero and four, the neural network classification was seen as correct when the difference between the neural network output and the score given by the physicians was smaller than 0.5. In other words, a classification was seen as correct when the rounded neural network output was exactly the same as that by the physicians.

Finding the optimal neural network

The severity of dyskinesia may be different for the different body parts, which is why the severity of dyskinesia has been rated for each body part separately. Furthermore, it is most likely that different parameters are required to detect dyskinesia for different body parts. For these reasons, different neural networks were trained for each body part (trunk, most affected leg and most affected arm). The complexity of a network depends on the number of units in the hidden layer and the number of input parameters. A complex network will result in a good performance on a training set but can give a poor performance on a test-set as a result of overfitting of the data-set, i.e. the network has a poor generalization performance. For this reason, neural networks with various numbers of hidden units and various numbers of input parameters were trained to assess the severity of the most dyskinetic leg, the most dyskinetic arm, and the trunk. For each number of hidden units the procedure of forward selection (Laar et al., 1999) was used to find the most valuable input variables to the neural network to assess the severity of LID. Forward selection means that we started with an empty set of variables, and add, one after another, the variable that causes the largest reduction of the mean square error (MSE) between the neural network output and the score given by the physicians. After each step, we look for the next most important variable, and so forth. This procedure provides insight into the variables that are used by the neural network and which characterize its performance. An advantage of this procedure is that it only adds

parameters that add to a better performance.

The optimal neural network was the network with the best generalization performance. The generalization performance of the network was tested by training the network with 80% of the data-set and testing the network with the remaining 20% of the data. This was done 50 times for different randomly selected sets of training and test-sets. The optimal architecture of the network was seen as the network, which gave on average the smallest MSE between the neural network output and the physician's rating on the test-set for the 50 randomly selected sets.

Results

In chapter three, we have presented the results of a neural network approach for the detection and rating of dyskinesia in patients with Parkinson's Disease. The performance of the neural network was considerably better than that of previous studies. The main results of that approach are shown in Table 4.2. Columns 2 and 3 show the MSE for movements of the arm, trunk, and leg between the rating given by the physicians and the rating by the neural network. Considering that dyskinesia is rated on an integer scale between zero (normal subjects) and four (severe dyskinesia), the MSE of 0.17, 0.14 and 0.15 for the arm, trunk and leg, respectively, is quite small. Any differences between the rating by the neural network and that by the physicians were smaller than one, indicating that in the worst case the rating by the neural network was in a class next to that given by the physicians. The fourth column shows the percentage of correctly classified data for 15-min intervals, indicating that the neural network somehow learned to detect and to classify the large majority of dyskinesias. More detailed information about these results is described in chapter 3.

Table 4.2. The MSE between the neural network rating and physicians rating.

	MSE (1-min interval)		**Percentage of correct**
Segment	Training-set	Test-set	**performance**
Arm	0.17±0.01	0.19±0.02	90.6
Trunk	0.14±0.01	0.14±0.02	97.5
Leg	0.15±0.01	0.18±0.03	93.4

The MSE for 1-minute intervals between the predicted rating by the neural network and the rating given by the clinicians (columns 2 and 3) for the arm, trunk and leg. Moreover, the last column gives the percentage of correctly predicted ratings in 15-min interval for the arm, trunk and leg on the test set.

Each body segment (trunk, most affected leg and most affected arm) was trained with a different neural network architecture. The optimal neural network is defined as the neural

network that gave the smallest mean square error on the test-set. This architecture was found by using the forward selection procedure for neural networks with various numbers of hidden units. Because dyskinesia usually lasts longer than 1 minute, the accuracy of detecting dyskinesia in 15-min intervals is better than in periods of 1 minute. However, because the network was trained on 1-minute intervals, we will mainly analyze the results of 1-minute interval periods. Therefore, the performance for 1-minute intervals shown in Figures 4.3, 4.5, and 4.9 is slightly less than reported in column 4 of Table 4.2, which refers to the performance on 15-min intervals.

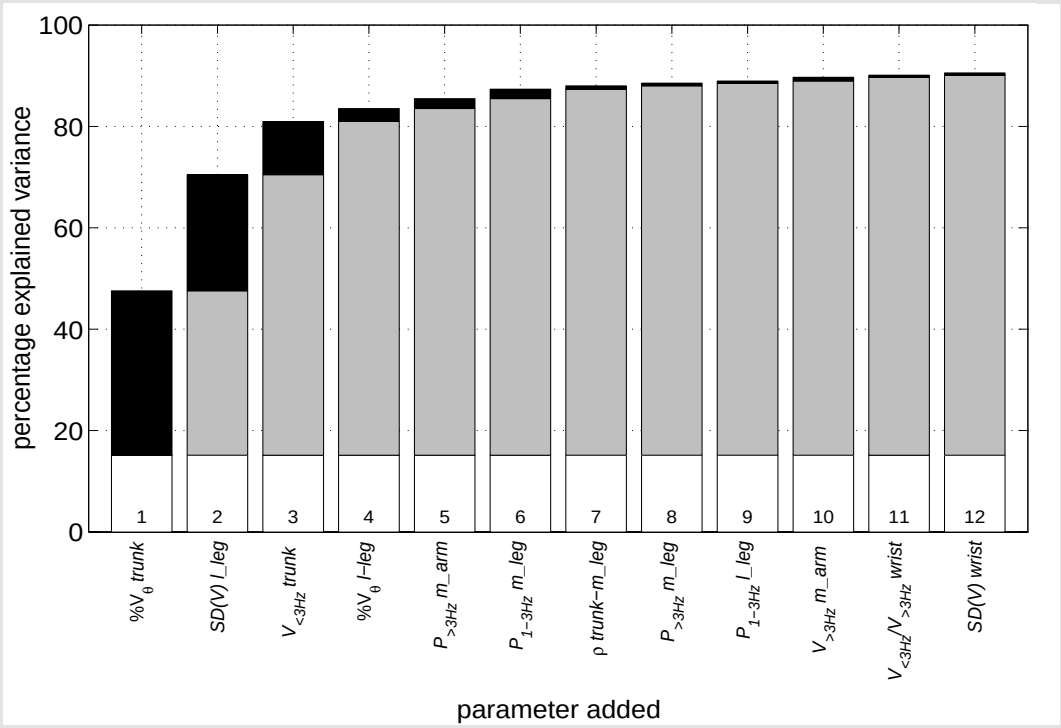

Figure 4.3. Most important parameters (see Table 4.1 for definition of parameters) for assessing the severity of dyskinesia for the trunk. Parameters added at each stage of the forward selection procedure and the percentage of the variance explained (total bars). The white part of the bars shows the percentage of variance due to the difference in rating by the physicians (integer values) and the neural network output (continuous value). The black part of each bar shows the performance due to including this parameter.

Assessing the severity of dyskinesia for the trunk

For the trunk, the best performing neural network had one hidden unit and required 12 input parameters to reach a correct classification performance of over 97%. The optimal neural network had one hidden unit, indicating that a linear classification was sufficient to assess the severity of dyskinesia for the trunk. Figure 4.3 shows the most important parameters, which contribute to the correct classification of dyskinesia for the trunk, in order of their contribution in explaining dyskinesia. Each bar indicates the performance on 1-minute intervals that is obtained by including a parameter in the neural network analysis. Because

physicians give an integer rating of 0, 1, 2, 3 or 4, while the neural network gives a continuous output between zero and four, there will hardly ever be a perfect match. The white segment of each bar shows the error due to this difference in rating output. The black part of the bar for each parameter indicates the increase of performance due to inclusion of that parameter.

The most important parameter for the classification of movements appears to be the percentage of time that the trunk is moving in a 1-minute interval ($\%V_\theta$ *trunk*). This parameter adds 32.4% to the correct performance of the neural network. Parameter $\%V_\theta$ *trunk* appeared to have the largest correlation with the neural network output (0.61), which explains why this parameter appears as the most important parameter to rate dyskinesia. The second most important parameter is the standard deviation of the velocity of the less affected leg ($SD(V)$ *lleg*), which adds another 22.9% to the performance. The third parameter in order is the power of the velocity signals in the range below 3 Hz ($\overline{V}_{<3Hz}$ *Trunk*), which adds an extra 10.5% to the performance. The contribution of the other

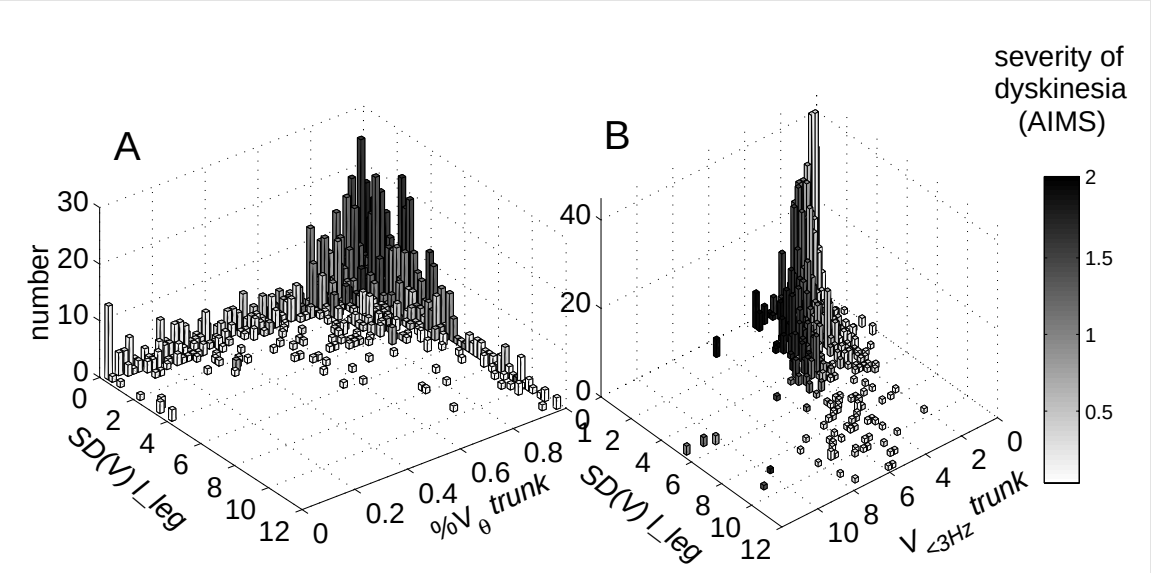

Figure 4.4. The relation between the three most valuable parameters and the rating by the neural network for the trunk. The gray scale indicates the severity of dyskinesia given by the neural network (see gray scale bar on the right). The height of the bar indicates the number of 1-minute intervals. Panel A shows the severity of dyskinesia as a function of the two most valuable parameters, percentage of time that the trunk is moving ($\%V_\theta$ *trunk*) and the standard deviation of the segment velocity of the less affected leg ($SD(V)$ *lleg*), respectively. Panel B shows the severity of dyskinesia as a function of the second and third most valuable parameter, $SD(V)$ *lleg* and the power of the segment velocity signal in the range below 3Hz ($\overline{V}_{<3Hz}$ *Trunk*), respectively.

nine parameters becomes gradually smaller, but is significant and explains an extra 9.6% to the correct performance of the neural network.

The three most valuable parameters together explain 81% of the variance (see Figure 4.3). The role of the three most valuable parameters can be appreciated by the data shown in Figure 4.4. Figure 4.4A shows that patients moving the trunk for a large fraction of time ($\%V_{\theta}$ *trunk*) and having a small value of the standard deviation of the segment velocity of the less affected leg ($SD(V)$ *lleg*), are most likely to have dyskinesia. Figure 4.4B shows the relation between the second ($SD(V)$ *lleg*) and third ($\overline{V}_{<3Hz}$ *Trunk*) most important parameters at the one hand and the dyskinesia rating by the neural network at the other hand. This figure shows that patients tend to suffer more from dyskinesia when the trunk movements with frequency components below 3Hz ($\overline{V}_{<3Hz}$ *Trunk*) are large relative to the standard deviation of the segment velocity of the leg ($SD(V)$ *lleg*).

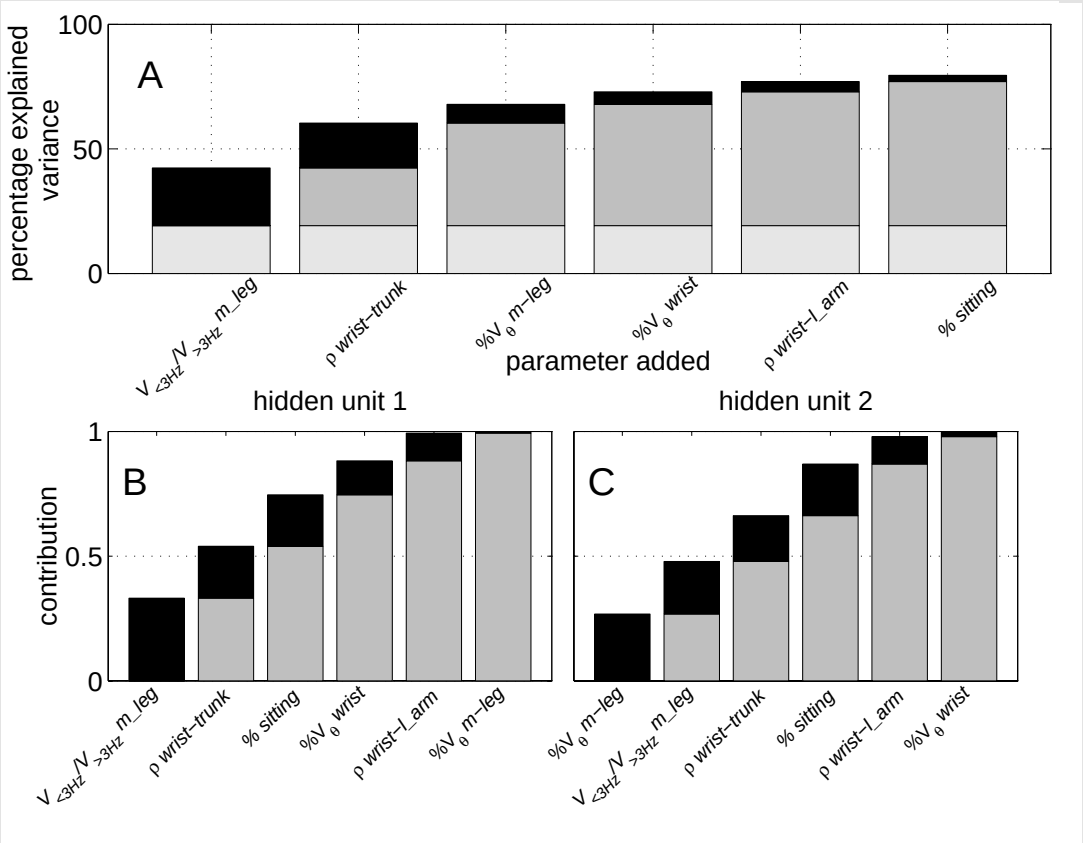

Figure 4.5. Panel A: The six most important parameters (see Table 4.1 for definition of parameters) for assessing the severity of dyskinesia for the arm as found using forward selection, and the percentage of the variance explained (total bars). The white part of the bar shows the percentage of variance due to the difference in rating by the physicians (integer values) and the neural network output (continuous value). Black part of the bars shows the percentage of variance explained by including the parameter. **Panels B and C:** The contribution of the input parameters to the output of the two hidden units of the optimal neural network for the arm (total bars). The contribution was determined using the forward selection procedure. The most important parameter is the first selected parameter. The black part of each bar indicates the increase of performance due to including the parameter.

Assessing the severity of dyskinesia for the arm

The optimal neural network for rating the severity of dyskinesia for the arm was a neural network with two hidden units and six input parameters. The order of the most important parameters and their contribution to the performance is shown in Figure 4.5A. The three most important parameters were $\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg*, $\overline{\rho}_{wrist-trunk}$ and $\%V_{\theta}$ *mleg*, adding 23.1%, 18.0% and 7.5% to the correct performance of the neural network for rating 1-min intervals. The other three parameters, added in the forward selection procedure, provided an increase in the performance of the neural network by another 11.6%.

Since the neural network has two hidden units, the relation between the input parameters and the network output is non-linear and not easy to appreciate. Both hidden units contribute in their own way to the severity of dyskinesia. The order of the most important parameters for each hidden unit is shown in panel B and C of Figure 4.5. The most important parameters for hidden unit 1 appeared to be the ratio between low and high frequencies of the most affected leg ($\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg*) and the cross correlation between wrist and trunk ($\overline{\rho}_{wrist-trunk}$). For hidden unit 2 the two most important parameters appeared to be parameters of the most affected leg ($\%V_{\theta}$ *mleg* and $\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg*).

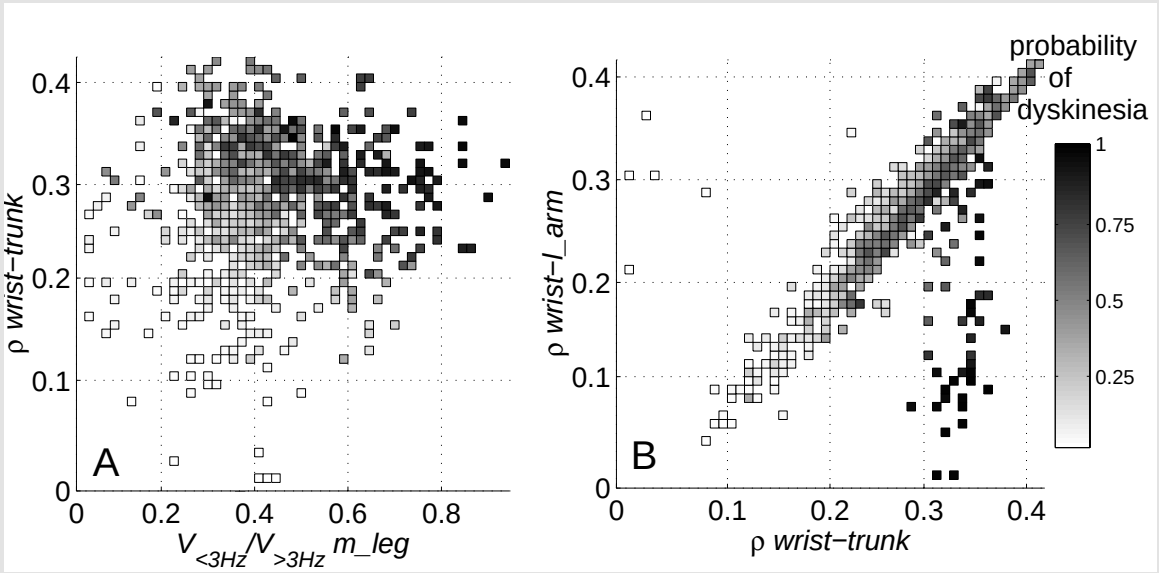

Figure 4.6. The probability that hidden unit 1 contributes to a rating of dyskinesia of the arm. Panel A shows the relation between the two most important parameters ($\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg* and $\overline{\rho}_{wrist-trunk}$) and the output of hidden unit 1. Panel B shows the relation between the two cross-correlation parameters ($\overline{\rho}_{wrist-trunk}$ and $\overline{\rho}_{wrist-larm}$) and the output of hidden unit 1. The gray scale indicates the probability that hidden unit 1 contributes to a rating of dyskinesia (black = dyskinesia, white = no dyskinesia).

Hidden unit 1 appeared to be most sensitive to variations in input parameters and was able to detect and rate mild dyskinesias. The output of hidden unit 1 depends on the

parameters $\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg*, $\overline{\rho}_{wrist-trunk}$, %*sitting*, $\%V_{\theta}$ *wrist* and $\overline{\rho}_{wrist-larm}$ (see Figure 4.5A). Figure 4.6 shows the relation between the two most important parameters ($\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg* and $\overline{\rho}_{wrist-trunk}$, panel A) and the relation between both cross-correlation parameters ($\overline{\rho}_{wrist-trunk}$ and $\overline{\rho}_{wrist-larm}$, panel B) for assessing dyskinesia. Hidden unit 1 will contribute to a rating of dyskinesia for the arm mainly when the movements of the most affected leg are predominantly at lower, rather than at higher frequencies (large value for parameter $\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg*), and for relatively larger cross-correlation values between wrist and trunk ($\overline{\rho}_{wrist-trunk}$) (see Figure 4.6A). A larger cross-correlation value between movements of the wrist and the trunk ($\overline{\rho}_{wrist-trunk}$) than between movements of the wrist and least affected arm ($\overline{\rho}_{wrist-larm}$) resulted in a higher probability that hidden unit 1 will contribute to a rating of dyskinesia (see Figure 4.6B).

Figure 4.7 shows the probability that hidden unit 1 contributes to a rating of dyskinesia, as a function of the percentage of time that the wrist was moving for patients who were sitting (black bars, %*sitting* was larger than 0.95) or for patients who were standing or walking (i.e. when %*sitting* was smaller than 0.05, gray bars). Hidden unit 1 mainly contributes to a rating of dyskinesia when patients are moving their wrist for a large fraction of time. Moreover, the probability, that a patient, who is moving the wrist for a long time, shows dyskinesia, is larger for a patient who is sitting than for a patient who is standing or walking.

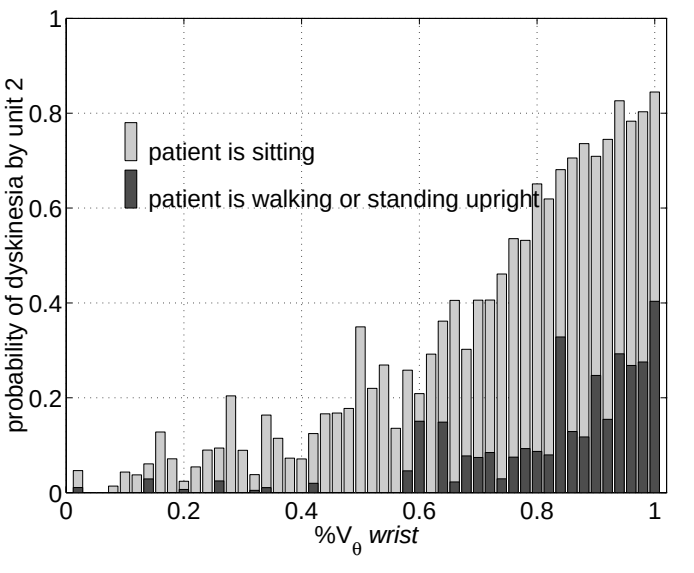

Figure 4.7. The probability that hidden unit 1 contributes to a rating of dyskinesia as a function of the percentage of time that the wrist was moving for patients who were sitting (gray bars) and for patients standing upright or walking (black bars) (0 = no dyskinesia, 1 = dyskinesia).

The output of hidden unit 2 depends mainly on the percentage of the time that the most affected leg is moving ($\%V_{\theta}$ *mleg*). It contributed to the rating of movements as normal (absence of dyskinesia) in 91% of the 1-min intervals and contributed to rating movements as dyskinesia when the most affected leg was moving for at least 88% of the time. This is illustrated in Figure 4.8, which shows the role of the second ($\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg*) and the

third ($\overline{\rho}_{wrist-trunk}$) most important parameter in rating dyskinesia. When the most affected leg is moving in at least 88% of the time, hidden unit 2 contributes to a rating of dyskinesia when these movements are predominantly at lower, rather than at higher frequencies (large value for parameter $\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg*) (see Figure 4.8A), and when the movements between wrist and trunk are uncoordinated (small value for parameter $\overline{\rho}_{wrist-trunk}$) (see Figure 4.8B). Hidden unit 2 appeared to contribute to a rating of dyskinesia when patients suffer from severe dyskinesia in the arm. This became obvious from the fact that the physicians rated a score of 2 or more for the arm in 71% of the 1-min intervals that were rated dyskinetic by hidden unit 2.

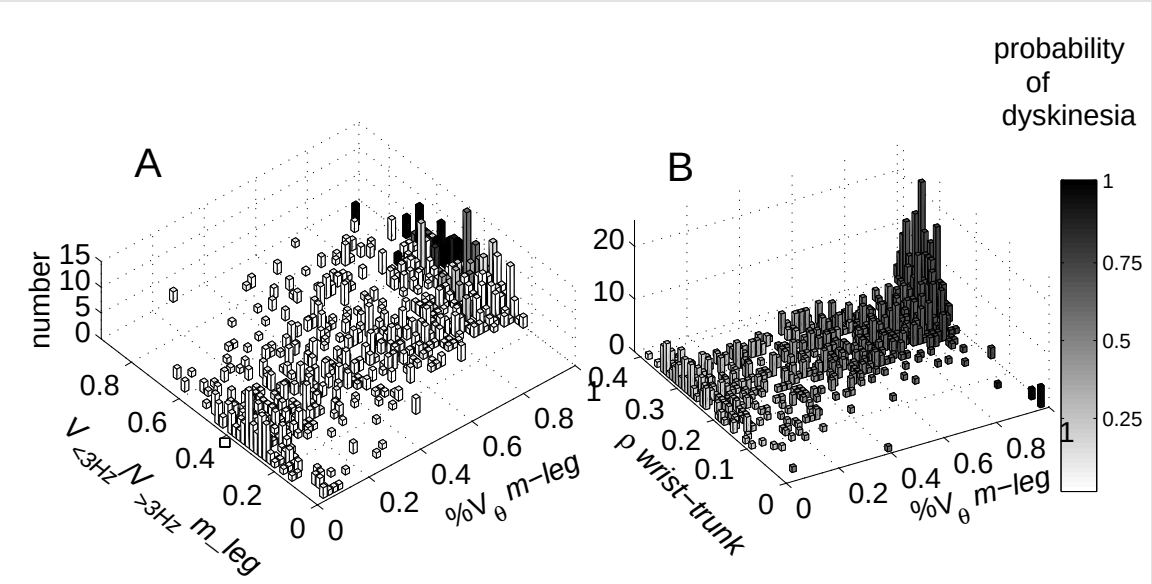

Figure 4.8. The relation between the three most valuable parameters and the output of hidden unit 2 of the network for assessing the severity of dyskinesia for the arm. The gray scale indicates the probability that hidden unit 2 contributes to a rating of dyskinesia (see gray scale bar on the right). Panel A shows the probability that unit 2 contributes to a rating of dyskinesia as a function of the two most valuable parameters of hidden unit 2 ($\%V_\theta$ *mleg* and $\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg*). Panel B shows the probability that unit 2 contributes to a rating of dyskinesia as a function of the most important parameter ($\%V_\theta$ *mleg*) and third valuable parameter ($\overline{\rho}_{wrist-trunk}$) of hidden unit 2.

Assessing the severity of dyskinesia for the leg

The optimal neural network for rating the severity of dyskinesia for the leg was a neural network with three hidden units and seven input parameters. Figure 4.9A shows the order of the most important parameters and their contribution to the correct classification of dyskinesia for the leg. The parameters $SD(V)$ *lleg* and $\%V_\theta$ *mleg* were the most important parameters and explained together 72.1% of the performance for rating 1-min intervals. The other five parameters added in the forward selection procedure, provided an increase of

13.4% to the performance.

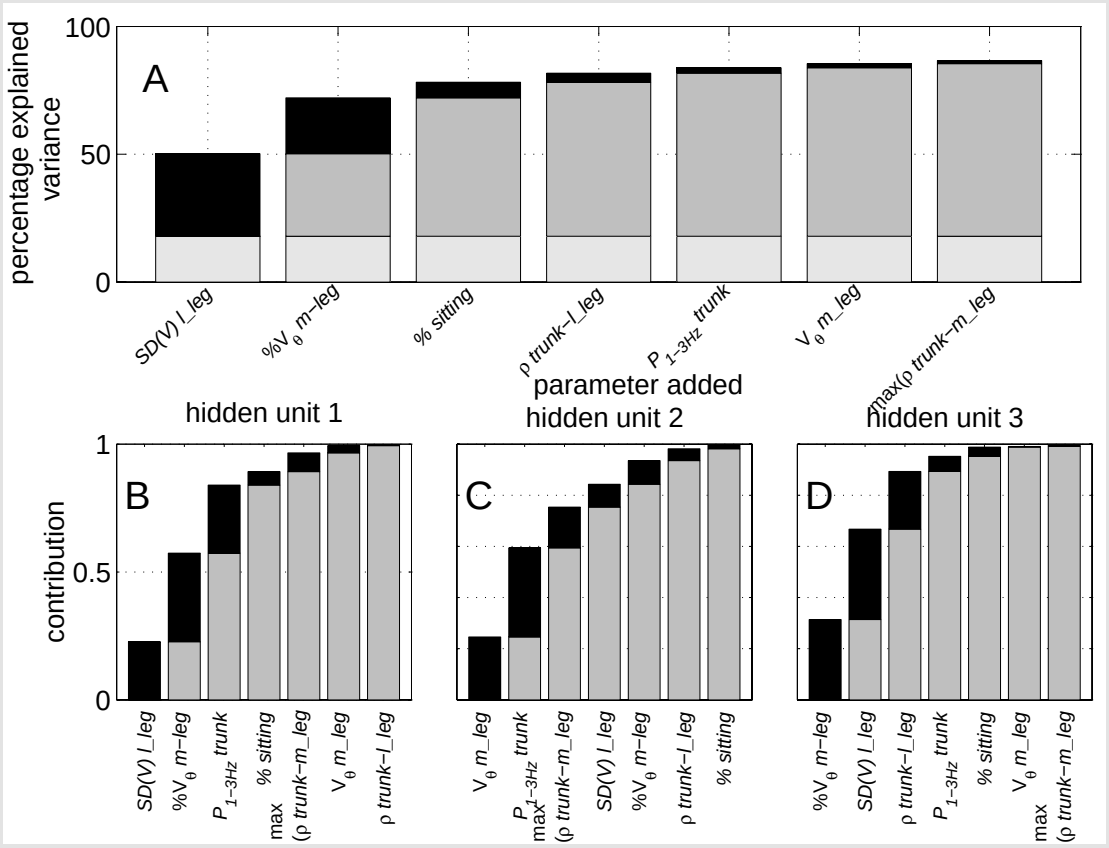

Figure 4.9. Panel A: Most important parameters (see Table 4.1 for definition of parameters) for assessing the severity of dyskinesia for the leg. Parameters added at each stage of the forward selection and the percentage of the variance explained. The white part of the bar shows the percentage of variance due to the difference in rating by the physicians (integer values) and the neural network output (continuous value). Black part of the bars shows the percentage of variance explained by including the parameter. **Panels B, C and D**: The contribution of the input parameters to the output of the three hidden units of the optimal neural network for the leg (total bars). The contribution was determined using the forward selection procedure. The most important parameter is the first selected parameter. The black part of each bar indicates the increase of performance due to including the parameter.

The neural network for the leg used three hidden units. The various parameters play a different role for each of the hidden units. The order of the most important parameters for each hidden unit is shown in panels B,C and D of Figure 4.9. Hidden unit 1 appeared to be most sensitive to variations in the input parameters and played a role in the rating of mild dyskinesias. The most valuable parameters of hidden unit 1 were the parameters selected in the early stages of the forward selection procedure (parameters $SD(V)\ lleg$, $\%V_\theta\ mleg$ and $P_{1-3Hz}\ trunk$). Figure 4.10 shows the probability, that hidden unit 1 contributes to a rating of dyskinesia as a function of the two most valuable parameters ($SD(V)\ lleg$ and $\%V_\theta\ mleg$,

panel A) and as a function of the first and third most important parameters ($SD(V)$ *lleg* and P_{1-3Hz} *trunk*, panel B). Hidden unit 1 contributes to a rating of dyskinesia when the standard deviation of the less dyskinetic leg has a small value and when the most dyskinetic leg is moving for a large fraction of time (see Figure 4.10A). In addition, the probability that hidden unit 1 contributes to a rating of dyskinesia increases for a higher power for frequencies in the range between 1 and 3 Hz of the trunk (see Figure 4.10B). The contribution of the parameter $\%sitting$ is that the probability of rating dyskinesia by the neural network increases for patients who are mainly sitting.

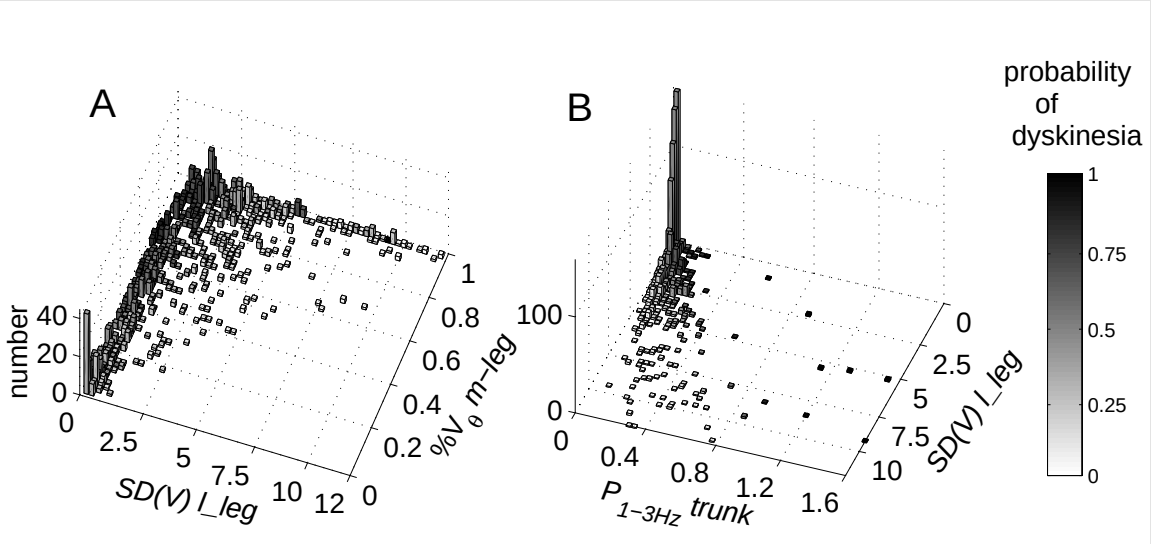

Figure 4.10. The relation between the three most valuable parameters and the output of hidden unit 1 of the network for assessing the severity of dyskinesia for the leg. The gray scale indicates the probability that hidden unit 1 contributes to a rating of dyskinesia (see gray scale bar on the right, black = dyskinesia, white = no dyskinesia). Panel A shows the probability that hidden unit 1 contributes to a rating of dyskinesia as a function of the two most valuable parameters ($SD(V)$ *lleg* and $\%V_\theta$ *mleg*). Panel B shows the probability that hidden unit 1 contributes to a rating of dyskinesia as a function of the most important parameter ($SD(V)$ *lleg*) and third valuable parameter (P_{1-3Hz} *trunk*).

Hidden unit 2 played a role in rating dyskinesia in a special case. The most valuable parameters of hidden unit 2 were the parameters selected in the later stage of the forward selection procedure ($\overline{V}_\theta$ *mleg*, P_{1-3Hz} *trunk* and $\max(\rho_{mleg-trunk})$, see Figure 4.9). Hidden unit 2 contributes to a rating of dyskinesia in only 7.6% of the 1-min intervals. The most valuable parameters for hidden unit 2 appeared to be the parameters $\overline{V}_\theta$ *mleg* and P_{1-3Hz} *trunk* and to a lesser extent the parameters $\max(\rho_{mleg-trunk})$, $SD(V)$ *lleg* and $\%V_\theta$ *mleg*. Hidden unit 2 contributes to a rating of dyskinesia when the mean velocity of the dyskinetic leg during moving is relatively small and when the power for frequencies in the

range between 1 and 3 Hz of the trunk is large.

Hidden unit 3 reveals a behavior similar to that by hidden unit 2 of the neural network for the arm. It contributes to the rating of dyskinesia only when a patient suffers from severe dyskinesia in the leg. Hidden unit 3 rated dyskinesia in 8% of the 1-min intervals and parameter $\%V_\theta$ *mleg* was the most important parameter. The other important parameters ($SD(V)$ *lleg* and $\overline{\rho}_{lleg-trunk}$) played only a role when the most affected leg was moving in at least 91% of the time. Hidden unit 3 appeared to contribute to a rating of dyskinesia when the leg was moving in at least 91 percent of the time, when the standard deviation of velocities of the less affected leg ($SD(V)$ *lleg*) was small. The probability that hidden unit 3 contributes to a rating of dyskinesia increases when the cross-correlation between the less affected leg and the trunk ($\overline{\rho}_{lleg-trunk}$) is relatively small for the large number of movements.

Discussion

In a previous study (Keijsers et al., 2003), we have presented the results of a neural network approach for the detection and rating of dyskinesia in patients with Parkinson's Disease. The neural network correctly classified dyskinesia or the absence of dyskinesia in 15-min intervals in 93.7%, 99.7% and 97.0% for the arm, the trunk, and the leg. In the present study, we focused on the role of the important parameters to assess the severity of dyskinesia and on how they contribute to a better understanding of movement characteristics in dyskinetic patients with Parkinson's disease.

A major advantage of using neural networks for the detection and rating of LID with the forward selection procedure to find the most relevant parameters is that this procedure searches for the most relevant parameters without any prior information and restriction. Our results showed that the most important parameters ($\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg*, $\%V_\theta$ *trunk* and $SD(V)$ *lleg* for arm, trunk and leg, respectively) were the best parameters for all segments, whatever the search algorithm. We also found that sometimes one parameter could be replaced by another parameter without large consequences for the performance of the neural network. This was usually related to the fact that parameters were highly correlated. For example, parameter $P_{>3Hz}$ *segment* gave almost the same performance as parameter $\overline{V}_{>3Hz}$ *segment*. We conclude that the selected parameters give a good representation of the important relevant parameters, which play a role in the assessment of the severity of dyskinesia.

For both the trunk and the leg the percentage of time that this segment was moving ($\%V_\theta$ *trunk* and $\%V_\theta$ *mleg*, respectively) and the standard deviation of the segment velocity of the less dyskinetic leg ($SD(V)$ *lleg*) gave the best performance. The importance of the percentage of time that a segment is moving is obvious, since a small percentage indicates

few movements and probably no dyskinesia, while a large percentage indicates many movements and thus a higher probability that the subject might suffer from dyskinesia. Parameter $SD(V)\,lleg$ appeared to play an important role to detect whether a patient is walking or not. In general ,dyskinesia is characterized by large values of $\%V_\theta\ segment$ and small values of $SD(V)\,lleg$ (see Figures 4.3, 4.7, 4.8, and 4.10). During walking, the percentage of time that a segment is moving is large like in dyskinesia. But in contrast to dyskinesia, parameter $SD(V)\,lleg$ showed large values for patients with normal walking behavior. The leg and to a lesser extent the trunk, are segments that are mainly involved in displacement of the whole body. The neural network is able to detect normal displacement (walking) by using parameters $\%V_\theta\ segment$ and $SD(V)\,lleg$. This might explain the importance of these two parameters and the good performance of assessing the severity of dyskinesia for the trunk and leg using these two parameters. For the arm, the parameter combination $\%V_\theta\ wrist$ and $\%sitting$ appeared to be the parameter combination which explained the largest part (70.6%) of the variance of the output of the most sensitive hidden unit (hidden unit 1). The role of parameter $\%sitting$ can be compared with the role of parameter $SD(V)\,lleg$. During sitting, subjects usually do not voluntarily move their arms continuously. Thus a large percentage of time that the wrist is moving when a patient is sitting implies a higher probability that a patient suffers from dyskinesia.

Previous studies in assessing dyskinesia focussed mainly on parameters in the frequency domain (Manson et al., 2000a; Hoff et al., 2001a). The results of these studies showed that dyskinetic movements were represented in the lower frequency bands (between 1 and 4 Hz, refs). In the present study, parameters $\overline{V}_{<3Hz}\ Trunk$, $\overline{V}_{<3Hz}/\overline{V}_{>3Hz}\ mleg$ and $P_{1-3Hz}\ trunk$ showed relatively larger values for patients suffering from dyskinesia (see Figures 4.4, 4.6, 4.8, and 4.10). Therefore, these results support the results of previous studies that dyskinesia is most dominant for movements in the lower frequency range. Moreover, dyskinesia occurs in frequencies significantly lower than the frequency domain of tremor, which is found above 3 Hz (Dubinsky, 1995; Hoff et al., 2001b). Therefore, dyskinesia can easily be distinguished from tremor.

The cross-correlation parameter played an important role in assessing the severity of dyskinesia, but its role is somewhat complicated. The role of the cross-correlation parameter was related to motor activity of the segments and the correlation of the segment velocity between the segments. Subjects showing small values of the mean cross- correlation (below 0.2) or large mean cross-correlation values (above 0.38) were not suffering from dyskinesia (see Figure 4.6), while patients showing mean cross-correlation values between 0.2 and 0.38 will have a larger probability that they were dyskinetic. Values of the mean cross-correlation below 0.2 are usually a result of little motor activity, while values of the mean cross-correlation above 0.38 are a result of a large number of well correlated voluntary movements. The large mean value of the cross-correlation corresponds to the observation by Soechting

et al. (1986), that joint velocities in elbow and shoulder covary during reaching and pointing movements to targets in 3D space. When the mean cross-correlation has a value between 0.2 and 0.38, parameter $\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg* appears to be an important parameter to indicate whether a subject is dyskinetic. Patients with mean cross-correlation values between 0.2 and 0.38 are most likely dyskinetic, when movements are predominantly at lower, rather than at higher frequencies (see Figure 4.6). The hidden unit, which contributed mainly to a rating of dyskinesia for severe dyskinesia (hidden unit 2 for the arm and hidden unit 3 for the leg), rated dyskinesia when the cross-correlation parameter has a relatively small value in conditions when there are a lot movements ($\%V_\theta$ large, see Figure 4.8). The role of the cross-correlation suggests that movements of body segments are not well coordinated in dyskinesia, which was also found in our previous study (Keijsers et al., 2000).

The neural network for assessing the severity of dyskinesia for the arm used two cross-correlation parameters, namely $\overline{\rho}_{wrist-trunk}$ and $\overline{\rho}_{wrist-larm}$. When parameter $\overline{\rho}_{wrist-trunk}$ has a value between 0.2 and 0.38 and when parameter $\overline{\rho}_{wrist-larm}$ was smaller than parameter $\overline{\rho}_{wrist-trunk}$, the probability that hidden unit 1 will rate dyskinesia increases (see Figure 4.6B). This means that it is most likely that subjects move voluntarily when wrist movements covary equally with movements of the trunk and of the less affected arm.

The neural networks for assessing the severity of dyskinesia for the arm and the leg used two and three units in the hidden layer, respectively. The neural network of both segments had one hidden unit (hidden unit 1 for leg and arm) that played a role in assessing mild dyskinesia using general characteristics of dyskinesia as described above. The other hidden units of the neural network were involved in detecting severe dyskinesia. Hidden unit 2 of the arm and hidden unit 3 of the leg were hidden units that rated only dyskinesia when a patient suffered from severe dyskinesia. For both segments, the hidden unit rated dyskinesia when the most dyskinetic leg was moving ($\%V_\theta$ *mleg*) in at least 90% of the time, while the other parameters did not imply stereotyped voluntary movements. The leg is a segment that is involved in voluntary movements mainly during displacements of the whole body like walking. Therefore, a lot of movement in the leg means either dyskinesia or displacement of the whole body. A distinction of the latter is made by a large value of parameter $SD(V)\ lleg$ and a relatively large value of the cross-correlation parameter.

For assessing the severity of dyskinesia of the leg and trunk, the neural network used mainly parameters of the trunk and leg (see Figures 4.3 and 4.9). However, for assessing the severity of dyskinesia of the arm, parameters of the most dyskinetic leg ($\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg* and $\%V_\theta$ *mleg*) were important (see Figure 4.5). Especially for severe dyskinesia, the rating was mainly based on the percentage of time that the most dyskinetic leg was moving (hidden unit 2). Presumably, severe dyskinesia in the leg implies at least mild dyskinesia in the arm, which was also described by Marconi et al. (1994). The advantage of using parameters of the leg instead of the arm is that the leg is less involved in voluntary movements than the

arm, except for walking. In case the leg is voluntarily moving, other parameters ($\overline{V}_{<3Hz}/\overline{V}_{>3Hz}$ *mleg* and $\overline{\rho}_{wrist-trunk}$) indicate that the patient may be voluntarily moving. Apparently, the neural network used parameters of the most affected leg to rate dyskinesia for the arm, based on the assumption that severe dyskinesia for the leg will imply at least mild dyskinesia for the arm (Marconi et al., 1994).

In our previous paper (Keijsers et al., 2003), we reported that neural networks could successfully detect dyskinesia and distinguish dyskinesia from voluntary movements. In this study, we have analyzed the optimal neural networks to find the important parameters that can detect and explain the severity of dyskinesia. The analysis showed that the percentage of time that a segment was moving is the most important parameter to detect dyskinesia. Other movement parameters are important, but in a different way for different limb segments. For the trunk and the leg, the standard deviation of the segment velocity of the less dyskinetic leg is important too. For the arm, the combination of the percentage of time, that the wrist was moving, had to be combined with the percentage of time, that a patient was sitting. In addition, dyskinesia differs from voluntary movements in the fact that dyskinetic movements tend to have lower frequencies than voluntary movements and in the fact that movements of different body segments are not well coordinated in dyskinesia.

Effect of levodopa dose on dyskinesia in advanced Parkinson’s disease with on-off fluctuations

Introduction

After several years of levodopa medication, many patients with Parkinson's disease (PD) suffer from levodopa induced peak-dose dyskinesia (LID) (Fabrini et al., 1987; Horstink et al., 1990a,b; Nutt, 1990; Marsden, 1994; Nutt et al., 1995). Among the many factors, that influence the occurrence of dyskinesia, the blood and striatal levels of levodopa play a pivotal role. In the early stages of levodopa treatment, the occurrence of peak-dose dyskinesia is associated with high levodopa concentrations, i.e. well above antiparkinsonian threshold. In a later stage, the occurrence of LID may turn into an "all-or-none" pattern, like the antiparkinson effect (Hardie et al, 1984; Nutt, 1990; Riley and Lang, 1993; Verhagen et al., 1997). In these later stage patients, dyskinesia occurs at levodopa levels slightly above or equal to the level required for an anti Parkinson effect. Verhagen et al. (1997) reported that incrementing the levodopa doses above 1.5 times the threshold dose (up to 3 times) did not further increase the severity of dyskinesia. Therefore, they concluded that fluctuating patients with a true on-off pattern could be treated with higher doses of levodopa than the dyskinesia threshold in order to increase the duration of action of the levodopa dose without the risk of increasing the severity of dyskinesia.

The result of Verhagen et al. (1997) that an increase in levodopa dose above 1.5 times the threshold dose did not cause an increase in the severity of dyskinesia may be influenced by the fact that the patients were assessed in a stable psychomotor situation and in a stable environment. Normally, the occurrence of dyskinesia is more likely during mental activity, stress, and social interactions with other persons. These effects are superimposed on the dyskinesia facilitating effect of levodopa. In addition, the severity of dyskinesia was assessed using clinical rating scales. A limitation of clinical rating scales is that these are subjective and cannot assess subtle differences in severity of dyskinesia. In conclusion, the results reported in the study by Verhagen et al. (1997) could be a result of the environmental setup and/or the assessment of dyskinesia.

In chapter 3, we developed a method to objectively and quantitatively assess the severity of dyskinesia in daily life. With this method the severity of dyskinesia for different doses of levodopa can be objectively evaluated in daily life. Another advantage of this method is that it gives a continuous output of values in the range between 0 and 4, so that small changes in the severity of dyskinesia can be detected. This cannot be done with the integer rating scale used by physicians, like the AIMS score in the study of Verhagen et al. (1997).

In line with our clinical experience with oral levodopa and dyskinesia we want to study the effect of levodopa doses on the severity of dyskinesia in a more daily life setting. The purpose of this study was to investigate whether increasing the dose of levodopa above the usual dose in Parkinson patients with on-off fluctuations would result in an increase of the

severity of LID while performing mental and motor daily life activities. The effect of the levodopa doses will be evaluated using the accelerometer signals and the objective quantitative method described in chapter three.

Methods

Patients

Nine patients with on-off fluctuations and with an all-or-none response to levodopa participated in this study. The protocol, patient information, and consent were approved by the Investigation Review Board of Rush University (Chicago, USA). All patients signed informed consent. Patients were invited to participate at three different days. Before each visit, patients took their anti-Parkinson medication as usual. At each visit, patients arrived at the same time of the day, 30 minutes before they had to take their next regular medication. After arriving at the clinic, the recorder and the accelerometers were attached to the patient as described in chapter 3. When patients were “off”, a test dose of levodopa medication instead of their regular levodopa medication was given. These test levodopa doses could be 1, 1.5 or 2 times the usual dose of the particular patient. The test doses were given double blind in randomized order. The monitoring started after the patient had taken the test levodopa medication and ended when LID had worn off or when the patient had performed several daily life tasks for at least 45 minutes during a dyskinetic period.

During the test-period, patients performed several mental and functional daily life activities. During each visit, all subjects performed at least the following tasks: taking off shoes, washing hands, making a phone call, chatting, reading a paper, counting, spelling backwards, relaxing, drinking from a cup, putting on a coat, and a peg-board test. These tasks were supplemented with several other tasks like making a sandwich, setting the table, playing a game, clearing the table. Furthermore, all patients were tested during two mental tasks, known to increase LID. The two mental tasks were counting backward and spelling words backward. These two mental tasks were performed in two conditions; when patients were sitting in a chair and standing upright. Patients performed the mental tasks for about two minutes. During these tasks, patients abstained from any voluntary movements and were asked not to suppress dyskinesia. The order of activities was about the same for each visit of a subject but was randomized over subjects. Patients were allowed to do the activities in their own way and at their own pace and they were free to take a rest between the activities at any time. A long test period and a large variety of activities have the advantage that patients are monitored in varying conditions from complete rest (relaxation) to voluntarily movements or mental tasks. The periods between activities were also analyzed and can be considered as an activity in which patients relax.

Data acquisition

Movements and postures of the patients were measured automatically using accelerometers and a portable data recorder as described in chapter 3. A set of three orthogonal accelerometers, to measure acceleration in all three directions in space, were placed at six different body positions. These six body positions are both upper arms, both upper legs, the wrist of the most dyskinetic side and the trunk. The accelerometers signals from these six sets of accelerometers were digitally stored on a portable recorder (Vitaport, TEMEC instruments, Kerkrade, The Netherlands). The recorder was worn on a belt around the patient's waist. Accelerometer signals were sampled at a frequency of 256 Hz., low-pass filtered using a moving averaging window, and stored on a removable memory card at a sample frequency of 64 Hz. The behavior of the patients was recorded on videotape.

Data analysis

While different tasks had a different duration and because the severity of LID could fluctuate during an activity, each task was divided in subsequent time intervals of one minute. Each one-minute interval was analyzed separately. These 1-minute intervals were used to compare and assess the severity of dyskinesia between the three visits.

First, the method developed in chapter 3 was used to assess the severity of LID. That method involved the use of neural networks to rate the severity of LID for the trunk, the most affected arm and leg for a series of one-minute intervals. This method could accurately assess the severity of dyskinesia. An advantage of this method is that it is able to distinguish between voluntary movements and dyskinesia. For a more detailed description, the reader is directed to chapter 3.

The second method to evaluate the severity of dyskinesia was done by analyzing movements based on three different variables. These variables were chosen based on the results from previous studies to assess the severity of dyskinesia (Manson et al. 2000a, Keijsers et al., 2001, Keijsers et al., 2003). These variables were the mean segment velocity ($\overline{V}$ *segment*), the percentage of time that a segment is moving ($\%V_\theta$ *segment*), and the mean signal power for frequencies in the range between 1 and 3 Hz (P_{1-3Hz} *segment*). Before any analysis, the accelerometer signals were filtered by a second-order-low-pass digital butterworth filter with a 3-dB cut-off frequency of 8 Hz. The mean segment velocity ($\overline{V}$ *segment*) was calculated by taking the square root of the sum of squares of the derivatives of the three accelerometer signals from a segment. The parameter $\%V_\theta$ *segment*, i.e. the percentage of time that a segment was moving, was defined as the percentage of time that the segment velocity was above a threshold of 0.05 m/s. The mean signal power for movements in the frequency range between 1 and 3 Hz (P_{1-3Hz} *segment*) was calculated using Fourier transformation. The signal power of a body segment was

calculated by taking the square root of the sum of squares of the signal power for movements in the frequency range between 1 and 3 Hz of the three accelerometer signals from that body segment.

The neural network ratings for one subject could not be calculated due to malfunctioning of the leg accelerometers. Therefore, the neural network analysis was done for 8 patients and the three parameters analysis for 9 patients.

Statistics

Differences in the severity of dyskinesia between the three doses were evaluated using the Friedman rank test. For the Friedman rank test, only the tasks that were performed during each visit could be used. Because patients were not always able to perform certain tasks during a visit, not all tasks were carried out during each visit. As a result, the number of tasks that were performed during each visit varied between 10 and 14 (mean 12; SD = 2). At first, the Friedman rank test was applied to the tasks performed during each visit and all 8 patients together for the neural network rating of the most affected arm, most affected leg, and the trunk, separately. In addition, the Friedman rank test was applied to the tasks performed during each visit and all 8 patients for the average neural network rating of the three segments. For the three variables $\overline{V}$ *segment* , $\%V_{\theta}$ *segment*, and $P_{1\text{-}3Hz}$ *segment*, the Friedman rank test was applied to the tasks performed during each visit and all 9 patients for all 6 segments, separately. In addition, the Friedman rank test was applied to the tasks performed during each visit, all 9 patients, and all 6 segments together. The Tuckey test was used for post hoc analyses.

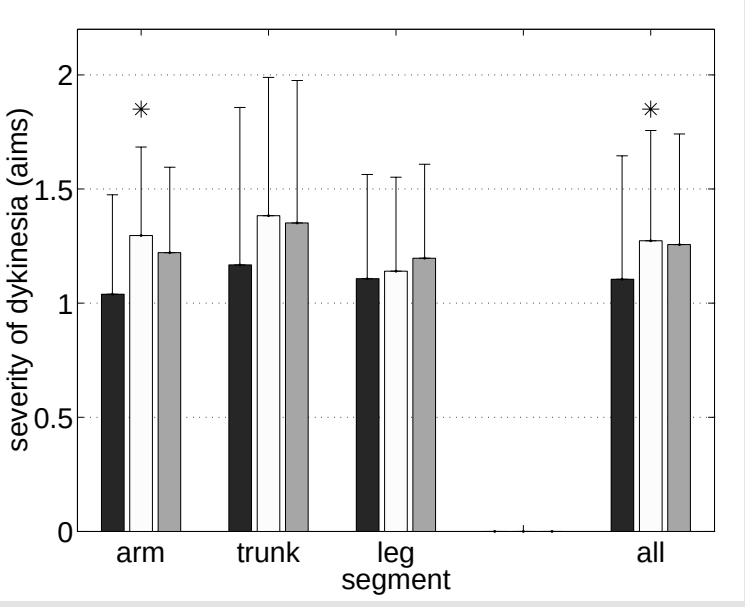

Figure 5.1. The average neural network rating of the severity of dyskinesia for the visits with 1 (black bars), 1.5 (white bars), and 2 (gray bars) times the threshold dose for the most affected arm, the trunk, the most affected leg, and for all three segments together. Stars (*) indicate significant difference between visits (P<0.05). Error bars represent standard deviations.

Differences between the levodopa doses for individual patients were evaluated using the Kruskall Wallis test. For this test, all 1-minute periods (about 40) were used and the severity of dyskinesia was referred to as the average rating for the most affected leg, the most affected arm, and the trunk by the neural network.

Results

Figure 5.1 shows the average rating of the severity of dyskinesia in the most affected arm, trunk, the most affected leg, and the average of the three segments by the neural network for the three levodopa doses. For the most affected arm and for the average of the three segments, the severity of dyskinesia was significantly smaller for the dose 1.0 than for the 1.5 and 2.0 dose (Friedman rank test : p=0.011 and p=0.047 for the most affected arm and for all segments together, respectively). The visits with 1.5 and 2 times the usual levodopa dose did not show a significant difference in the severity of dyskinesia.

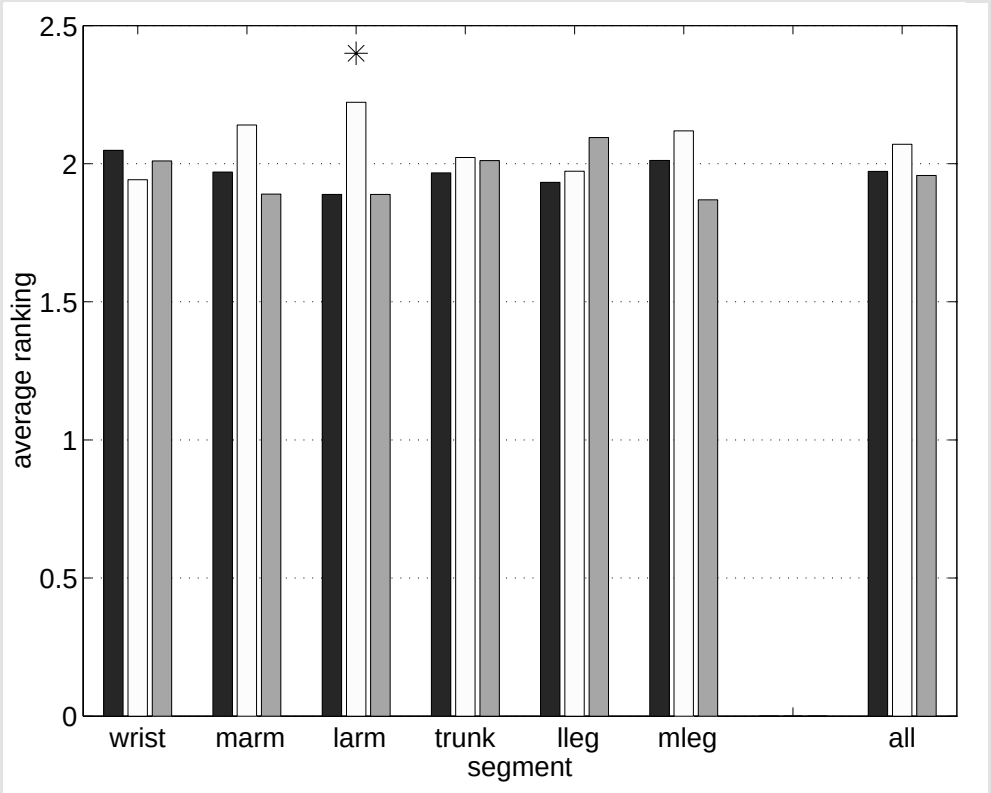

Figure 5.2. The average rankings of the severity for the visit with 1 (black bars), 1.5 (white bars), and 2 (gray bars) times the threshold dose for the 6 segments separately (wrist, most affected arm, les affected arm, trunk, les affected leg, and most affected leg) and all 6 segments together. Stars (*) indicate significant differences between visits (P<0.05).

Figure 5.2 shows the average ranking for the severity of dyskinesia for the visits with

1, 1.5 and 2 times the usual levodopa dose based on the variable P_{1-3Hz} *segment* . The average rankings for the 6 segments separately and for all segments together for the variables $\overline{V}$ *segment* and $\%V_\theta$ *segment* were very similar to the results for the variable P_{1-3Hz} *segment*. If the severity of dyskinesia would linearly depend on the dose of levodopa given for all patients, the average ranking would be 1, 2 and 3, for increasing dose. The variable P_{1-3Hz} *segment* showed a significantly higher rating for the 1.5 dose than the 1 and 2 dose for the less affected arm (p=0.04), which was also the case for the variables $\overline{V}$ *segment* (p=0.01) and $\%V_\theta$ *segment* (P=0.04). The rating of the severity of dyskinesia for the less affected arm for the visits with 1 and 2 times the usual levodopa dose did not differ significantly (see Figure 5.2). The variables $\overline{V}$ *segment* and P_{1-3Hz} *segment* (see Figure 5.2) did not show a significant difference between the levodopa doses for segments other than the less affected arm. The variable $\%V_\theta$ *segment* showed also a significantly higher rating for the 1.5 dose than for the 1 and 2 dose for the most affected arm (p=0.04) and for all segments together (p=0.03). For these reasons, we conclude that the variables $\overline{V}$ *segment* , $\%V_\theta$ *segment* , and P_{1-3Hz} *segment* could not demonstrate a relation with the administered levodopa dose and the severity of LID.

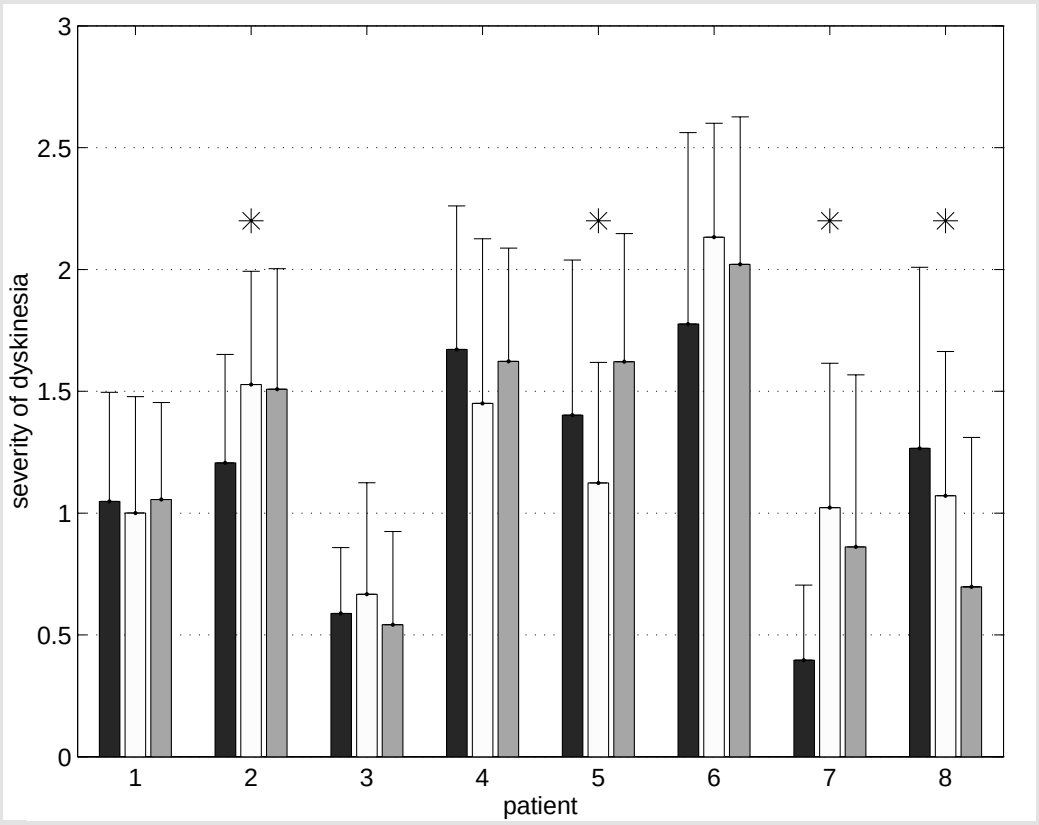

Figure 5.3. The average neural network rating of the severity of dyskinesia for the visits with 1 (black bars), 1.5 (white bars), and 2 (gray bars) times the threshold dose for each individual patient. Stars (*) indicate significant differences between visits (P<0.05). Errors bar represent the standard deviations.

The Kruskall-wallis test revealed a significant difference for dyskinesia at three levodopa doses for 4 of the 8 patients. Figure 5.3 shows the average severity of dyskinesia for the 8 patients for the visit with 1, 1.5 and 2 times the usual levodopa dose. As can be seen in Figure 5.3, patients show large individual differences in their responses to different levodopa doses.

Discussion

In this study, the effect of levodopa dose on the severity of dyskinesia was evaluated during mental and motor daily life activities. Patients took double blind a dose equal to 1, 1.5, and 2.0 times the usual levodopa dose at three different visits. Patients showed the smallest severity of dyskinesia for the usual (1.0) levodopa dose. The severity of dyskinesia was larger for the 1.5 and 2.0 times the usual levodopa dose compared to the threshold dose whereas the severity of dyskinesia did not differ significantly between 1.5 and 2.0 times the levodopa dose. The response of patients showed large inter-individual differences to different levodopa doses.

A previous study by Verhagen et al. (1997) on the effect of supra-threshold levodopa administration on dyskinesia, reported that dyskinesias increase steeply to attain their maximum values at approximately 1.5 times the levodopa threshold and then reach a plateau despite further increments. The results of the present study confirm this dose-response relation for the dyskinesiogenic effect of levodopa reported by Verhagen et al. (1997). In addition, an increase in the severity of dyskinesia of approximately 1 for all segments together (the 4 extremities and the axial) for 1.5 threshold levodopa dose compared to the threshold dose was found by Verhagen et al. (1997) In this study, an average increase in dyskinesia between 1 and 1.5 threshold dose of approximately 0.25 for each of the three segments rated by the neural network was found (see Figure 5.1). An average increase of approximately 0.25 for each segment suggests an increase of approximately 1.25 for all segments together which is in agreement with the increase found by Verhagen et al. (1997). Therefore, we can conclude that the increase in severity was of equal magnitude in both studies. These findings suggest that the differences in experimental setup between the present study and the study of Verhagen (1997) did not result in clear differences in the results of both studies.

The main differences in experimental setup between the present study and the study of Verhagen et al. (1997) were administration of levodopa (oral versus intravenous), environmental situation (daily life activities versus controlled), and the procedure of assessment of dyskinesia (neural network rating versus physician's rating). An advantage of intravenous levodopa administration is that it will result in controlled blood levodopa levels.

The blood levodopa level in oral administration depends to a large extent on the absorption of levodopa in the duodenum and the transport through the stomach (Wade et al., 1973). The transport through the stomach is delayed by large meals, low pH and anticholinergic drugs and effects the levodopa plasma levels (Rivera et al., 1970; Fermaglich and O'Doherty, 1972; Nutt et al., 1984; Kurlan et al., 1988; Bredberg et al., 1993). Despite the oral administration of levodopa in this study, the general results were in agreement with the intravenous study. However, the large individual differences in response found in this study could be a result of the oral administration of levodopa.

It is generally known that stress and/or motor activities have an effect on the severity of dyskinesia. Patients often showed a small increase in severity of dyskinesia in tasks such as making a phone call, spelling and counting but this was irrespective of levodopa dose. The present findings together with the previous results of Verhagen et al. (1997) in a stable psychomotor situation suggest that the effect of stress on dyskinesia is not superimposed on supra-threshold levodopa doses.

The neural network rating for dyskinesia has the benefit that its output is a continuous function of the severity of dyskinesia and that it distinguishes voluntary movements from dyskinesias (Keijsers et al., 2003). In contrast to the neural network, the three variables ($\%V_{\theta}$ *segment*, $\overline{V}$ *segment*, P_{1-3Hz} *segment*) did not demonstrate any relation with the levodopa dose. In a previous study, we demonstrated that it will be impossible to distinguish voluntary movements from dyskinesia in daily life by using only variables that indicate the amount of movement such as the mean segment velocity ($\overline{V}$ *segment*), the percentage of time that a segment is moving ($\%V_{\theta}$ *segment*), and the mean signal power for frequencies in the range between 1 and 3 Hz (P_{1-3Hz} *segment*). The difference in results between the neural network and the three variables suggest that several variables and their mutual linear and nonlinear connections as used in the neural network method provide a more reliable assessment of the severity of dyskinesia in daily life settings.

The small increase in dyskinesia between 1 and 1.5 times the usual levodopa means that the levodopa dose has still a pivotal role in managing dyskinesias in daily life. However, the large individual differences in the responses suggest that other, as yet not fully known, factors also play an important role on the severity of dyskinesia. This study could not decide which factors were responsible for the large individual differences and which mechanisms may underlie the equal dyskinesia response for levodopa doses above 1.5 times the threshold dose.

Differential progression of proprioceptive and visual information processing deficits in Parkinson's disease

Adapted from Keijsers NLW, Admiraal MA, Cools AR, Bloem BR, Gielen CCAM. submitted

Introduction

The accuracy of pointing movements depends to a large extent on the availability of visual and proprioceptive information. When pointing to remembered visual targets in complete darkness, proprioceptive information provides the most reliable source of information about finger position (van Beers et al., 1999, 2002). With visual feedback of finger position, the accuracy of pointing increases, especially in the direction of azimuth and elevation and to a lesser extent also in depth (depth refers to radial direction relative to the observer) (van Beers et al., 2002). These properties of proprioceptive and visual information processing in man explain why errors for pointing to remembered visual targets have 3-D ellipsoidal distributions (Soechting and Flanders, 1989a, 1989b; McIntyre et al., 1997, 1998) with the long axis directed towards the subject and why pointing becomes more accurate with the availability of visual feedback (Admiraal et al., 2003).

Pointing to remembered visual targets has previously been used to investigate deficits in sensory information processing in patients with Parkinson's Disease (PD). PD patients have well known movement abnormalities including bradykinesia (slowness of movement), hypokinesia (lack of movement), akinesia (inability to initiate a movement), tremor and rigidity. In addition to these well-known movement abnormalities, recent studies suggest that PD patients also have deficits in the processing of sensory inputs, particularly in the processing of proprioceptive inputs (Schneider et al., 1987; Klockgether et al., 1995; Rickards and Cody, 1997; Jobst et al., 1997; Zia et al., 1999; Khudados et al., 1999; Lewis and Byblow, 2002). For example, PD patients were less sensitive in identifying the occurrence and direction of externally imposed movements Schneider et al., 1987). Furthermore, PD patients produce larger errors than controls in static joint position sense of the elbow (Zia et al., 1999). PD patients make larger errors than normal subjects in reproducing a passive finger movement (Zia et al., 1999) and make larger errors in matching the position of a passively moved finger to the position of a visual target (Klockgether et al., 1995). Because muscle spindle sensitivity is normal in PD (Delwaide and Gonce, 1993), the impaired joint position sense in PD seems primarily of central neural origin. This hypothesis is supported by the finding of reduced sensory-evoked brain activations in cortical (parietal and frontal) and subcortical (basal ganglia) areas in PD patients using positron emission tomography (Boecker et al., 1999). Furthermore, a reduced level of intracortical inhibition was found in PD patients, which also suggested an abnormal influence of afferent input on corticomotor excitability (Lewis and Byblow, 2002). In addition to these findings in PD patients, Filion et al. (1988) reported an increase in the number, magnitude, and loss of specificity of responses in the basal ganglia of MPTP-treated monkeys to passive limb movement. The latter study suggests, that deficits in motor performance in PD are, at least partly, due to deficits in the processing of sensory (mainly proprioceptive) information in the

basal ganglia.

Animal studies have shown that the ability to use sensory information depends on the degree of dopamine deficits in the Substantia Nigra (Cools et al., 1993; Martens et al., 1996). A minor dopamine deficit in the caudate nucleus only affects its first output station, the substantia nigra pars reticulata. Animals with such a minor dopamine deficit showed a reduction of the ability to use static proprioceptive stimuli in motor control (Cools et al., 1983; Jaspers et al., 1984, 1989). Such animals could only switch between motor programs when external visual cues were available to direct their movement. Therefore, proprioceptive information processing was affected following minor dopamine deficits, but this could be overcome with the use of visual information. More severe dopamine deficits in the Substantia Nigra produce a GABA hyperactivity in the deeper layers of the Colliculus Superior (Scheel-Kruger, 1985). Animals with a mild GABA hyperactivity in the Colliculus Superior showed a reduced ability to use visual information in switching between motor patterns (Gelisssen and Cools, 1986, 1987a,b, 1988). Extrapolating these results to humans suggests that in an early stage of PD (a mild dopamine deficit), patients will produce larger errors in pointing than age-matched controls in a condition without visual information, but may perform equally well with the availability of visual feedback. However, with ongoing progression of PD, we hypothesize that patients will produce increasingly larger errors, even in conditions with visual information.

Previous studies on pointing to remembered visual targets in PD have reported that PD patients point less accurately than normal subjects in complete darkness while they are almost as accurate with visual guidance (Adamovich et al., 2001; Klockgether et al., 1994; Flash et al., 1992; Ketcham et al., 2003). The pointing movements in these studies were only studied in two dimensions (Klockgether et al., 1994; Flash et al., 1992; Ketcham et al., 2003) or in 3D, but then with a limited number of movements to a single target (Adamovich et al., 2001). Due to the limited number of movements, an accurate determination of the constant and variable error in depth, azimuth and elevation could not be done. Moreover, these studies did not test the effect of severity of the disease on the accuracy of pointing.

In this study we have investigated the constant and variable errors of pointing movements to remembered visual targets in PD patients with various degrees of severity of the disease and in a group of age-matched controls. All subjects were tested in two conditions: pointing to a remembered visual target in complete darkness (DARK) and in the presence of an illuminated cubic frame with a light attached to the tip of the index finger (FRAME). The idea behind these experiments was 1) that any differences in pointing errors in the two conditions reflect the effect of visual feedback in pointing by the subject and 2) that any differences in accuracy of pointing in the two conditions in patients with various degrees of PD may reveal insight into the progressive effect of the disease on proprioceptive and visual information processing.

Table 6.1. Characteristics of PD patients

No.	Sex	Age	Disease Duration	H & Y stage	UPDRS score	Medication (per 24 hours)
1	M	71	1	2	18	-
2	M	74	5	2	47	-
3	M	54	4.5	3	38	LC(3x125), DRA (4x0.25)
4	M	67	2	2.5	54	-
5	M	52	4	2	35	-
6	M	56	12	2	33	DRA(3x1), S(2x5)
7	F	72	1.5	2	30	LC(3x62.5)
8	M	37	1.5	2	37	DRA(3x2)
9	M	58	4	2.5	32	-
10	M	72	7	2.5	43	LC(5x 137.5), DRA(3x5), Am(2x100)
11	F	63	1.5	2	26	An (7x2)
12	M	52	16	3	68	LC (9x125), DRA (4x4), Am(2x100), C(4x200), S(2x5)
Mean		60	5.0	2.3	38	
SD		11	4.7	0.5	13	

H & Y = Hoehn and Yahr, medication: LC – levodopa / carbidopa ; DRA – dopamine receptor agonist; Am - Amantadine; C - anticholinergic; S – Selegeline

Methods

Patients

This study included 12 patients (10 male, 2 female, age 60 ± 11 years) who fulfilled the UK Brain Bank criteria for idiopathic PD (Hughes et al., 1992). All patients sustained a clear beneficial response to treatment with levodopa or a dopamine agonist. Controls included 10 healthy elderly subjects that were matched for age and sex (8 male, two female, age 61 ± 10). Five patients had no anti-parkinsonian medication, whereas seven patients had anti-parkinsonian medication in various combinations. The clinical details of the PD patients are given in Table 1. All subjects in this study (both normal subjects and PD patients) had normal vision (or corrected to normal) and did not have oculomotor problems (except for minimal saccadic intrusions during smooth pursuit) or neurological disorders other than PD. We also excluded patients with dementia, a postural tremor of the arms within the first few seconds of assuming a sustained posture (score $\geq$1 on item 21 of the Unified Parkinson's Disease Rating Scale (UPDRS) (Lang, 1995)) or significant dyskinesias (score >2 on the Modified Dyskinesia Rating Scale) (Goetz et al., 1994). We did not exclude patients with a

"resetting" rest tremor of the arms that became apparent only after several seconds of assuming a sustained posture, *i.e.* well after completion of each individual pointing movement. Patients were examined in a defined "off state" after overnight withdrawal of all antiparkinson medication (Defer et al., 1999). All patients had predictable end-of-dose wearing off effects and the interval between start of the experiments and intake of the last medication was at least 12 hrs. Although it may be necessary to withdraw antiparkinson medication for several days to entirely eliminate treatment effects, this approach allows for assessment of parkinsonian manifestations in a fairly stable "off" state (Defer et al., 1999).

Immediately before the experiments, the patients were clinically examined by an experienced movement disorders specialist (BRB) using the modified Hoehn and Yahr stages and the Unified Parkinson's Disease Rating Scale (UPDRS) (Lang, 1995) (Table 1). The experiments were approved by the Medical Ethical Committee of the University Medical Center of Nijmegen. All subjects gave witnessed and signed informed consent according to the Declaration of Helsinki, but the participants were not informed about the specific purposes of the study.

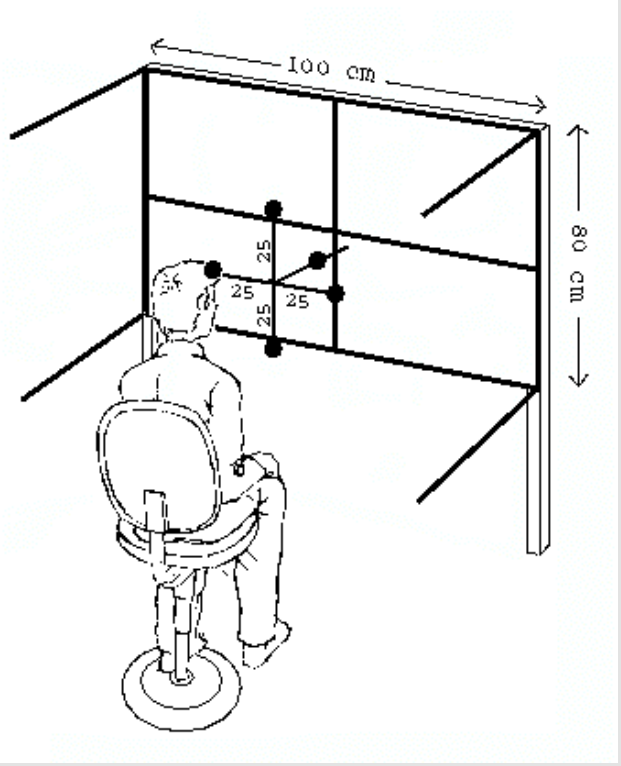

Figure 6.1. Schematic overview of the experimental setup. Subjects were seated upright facing a flat backboard. During target presentation, the center of the cross was at a distance of about 40cm in front of the subject (45cm in front of the backboard) and at a position halfway between the line between the subject's shoulder and the eyes. Four targets were on the vertices of the cross, which were 25cm from the center of the cross. A fifth target was placed on a stick, 25cm from the center of the cross. The illuminated optic fibers in the FRAME condition are presented as bold lines.

Experimental setup

Figure 6.1 shows a schematic overview of the experimental setup. Subjects were seated upright in a chair with their hands on their knees facing a flat backboard (100cm wide

x 80cm high) placed at a distance of about 85cm in front of the subjects shoulder. Subjects had to point to the position of one out of five targets, which were presented as illuminated light-emitting-diodes (LEDs) on a metal cross. The cross with targets was positioned reproducibly at a position between the subject and the board with a moveable stick. For each trial one of the LEDs was switched on for one second. After offset of the target LED, the cross was removed by the experimenter such, that the subject could point to the remembered target without touching the metal cross or stick. During target presentation, the center of the cross was at a distance of about 40cm in front of the subject's shoulder (45 cm in front of the backboard) and at a position halfway between the line between the subject's shoulder and the eyes. Four LEDs were positioned on the vertices of the cross, at a distance of 25cm from the center of the cross. A fifth LED was placed on the stick, 25cm behind the center of the cross and 20cm in front of the backboard. All subjects could easily reach all targets without full extension of their arm.

Each target presentation consisted of illumination of one of the five red LED's for a period of 1 second. Onset of the LED-target marked the start of a trial. When the target LED was switched off, the target was quickly removed. Two seconds after target offset, an auditory signal (a tone of 1000 Hz) instructed the subject to start the pointing movement to the remembered target position. Subjects were explicitly instructed to wait for the auditory signal before starting the pointing movement, and to keep the index finger at the position of the remembered target for about half a second before they returned to the initial position.

All subjects made pointing movements to remembered visual targets with their right hand except for two PD patients who pointed with their left hand. These two patients showed almost no signs of PD on their right side but had clear signs on their left side. For these two patients, targets were presented at mirror-symmetric locations relative to the position between the left shoulder and the eyes instead of the regular position between the right shoulder and the eyes.

Subjects were tested in two conditions: pointing to the remembered target in complete darkness (DARK) and pointing in the presence of an illuminated cubic frame with a continuously lit red LED attached to the tip of the index finger (FRAME). In this FRAME condition, a well-defined visual environment was shown to the subject by means of illuminated optic fibers (diameter 2mm) along the edges of the blackboard (100cm wide x 80cm high), with an illuminated cross centered in the middle (100cm wide x 80cm high) and with four 60 cm long illuminated optic fibers orthogonal to the backboard (see Figure 6.1). The frame was visible at all times in the FRAME-condition and the targets were presented within the illuminated cubic frame.

The targets were presented in randomized order in blocks of twenty trials. Subjects started with a block of 20 test trials in the DARK condition and a block of 20 test trials in the FRAME condition in order to become familiar with the experiment. Data of these test trials

were not included in further data analyses. Thereafter, subjects were tested in 10 blocks of 20 trials, each randomized over the two conditions. This means that each target was presented 20 times to the subject in both the FRAME and DARK condition. A block of 20 trials lasted about 4 minutes, and after each block, the room lights were switched on for at least 30 seconds to avoid dark adaptation during the test.

Position of the Subject's head, shoulder, arm, and index finger as well as the target position were measured with an OPOTRAK 3020 system (Northern Digital). This system measures the three-dimensional position of infrared-light-emitting-diodes (ireds) with a resolution better than 0.2 mm within a range of about 1.5 m^3. Ireds were placed on the subject's shoulder (acromion), elbow (epicondylus lateralis), and on the tip of the index finger. The position of the LED targets was measured by ireds directly placed on each of the LED's. Subjects were free to rotate their head and were wearing a helmet with six ireds, so that the 3D head orientation could be calculated. Before each experiment, subjects had to look at the OPTOTRAK system with 2 ireds on each of the two eyes. In this way, the position of the eyes relative to the ireds on the head was known. This information was used to calculate the positions of the eyes and the cyclopean eye relative to the orientation of the head in 3D. The position of the tip of the index finger was measured by means of an ired attached to a thimble on the index finger. This thimble also contained a visible red LED that provided the subject with feedback on finger position in the FRAME condition.

Data analysis

Pointing position was defined as the position of the ired on the tip of the index finger at the end of the pointing movement towards the target. Both the constant errors and the variable errors were computed. The constant error is defined as the difference between the target position and the average of all pointing positions to that target. It reflects the general error in planning and execution of the pointing movement. The variable error reflects the distribution of the pointing positions towards a target relative to the average pointing position to that target and reflects the noise in planning and execution. The distribution of the pointing positions for each target is described by the 3-D covariance matrix S_i:

$$S_i = \frac{\sum_{j=1}^{n} \delta_j^i \left(\delta_j^i\right)^T}{n-1}$$

where n is the number of trials to target i and $\delta_j^i = p_j^i - \overline{p}^i$ is the deviation of the finger position p_j^i for trial j to target i relative to the mean pointing position $\overline{p}^i$ to target i. The three orthogonal eigenvectors of the covariance matrix S_i describe the orientations of the variable errors. The corresponding eigenvalues of the matrix give the size of the variable

error along the eigenvectors. The total variable error for pointing to a target was computed as the volume of the ellipsoid with the eigenvectors as the three orthogonal axes, each with the length of the corresponding eigenvalue of the covariance matrix for that target. The eigenvalues of the covariance matrix S_i can be scaled to compute the limits that contain 95% of the data (For details, see Mcintyre et al., 1997).

Spatial components of the constant errors were computed in a viewer-centered coordinate system with distance (overshoot/undershoot), azimuth (left/right) and elevation (upward/downward), relative to the cyclopean eye. Spatial components of the variable error were evaluated using the eigenvectors of the covariance matrix. The eigenvector mostly directed towards the eyes will be referred to as the direction of variable error in radial distance. For most targets, this eigenvector was the eigenvector with the largest eigenvalue in both the DARK and FRAME condition (see Figure 6.2). The eigenvector that was most dominant in the horizontal (vertical) plane will be referred to as the direction of the variable error in azimuth (elevation).

One control subject showed a constant error in the DARK condition that exceeded the average constant error of control subjects by 2.6 standard deviations. For this reason, this outlier was left out of the statistical analysis, resulting in a total of 9 control subjects and 12 PD patients. Differences in constant errors and variable errors between controls and PD patients were tested using *three way* ANOVA with one *between groups* factor (controls versus PD patients) and two *within* factors (condition: DARK and FRAME, and target location (five targets)). *Two way* ANOVA with one *between groups* factor (controls versus PD patients) and one *within* factor (target location) was used to test for differences between controls and PD patients in the DARK and in the FRAME condition. A Tukey test was used for post hoc analyses. Correlation analyses were conducted to assess the relations between disease severity (UPDRS score) and error size.

Results

Group analysis

Figure 6.2 illustrates the main findings for pointing to remembered targets in the FRAME condition for control subjects and for PD patients. It shows the pointing positions to remembered targets, the constant error (average pointing position relative to target position) and the variable error (distribution of the pointing positions relative to the average pointing position) for a control subject (left panels) and for a severe PD patient (UPDRS score of 68). The distribution of the pointing positions of the control subjects are characterized by an ellipsoid with the long axis of the distribution oriented toward the subject. This finding was particularly obvious for the FRAME condition. The variable and constant errors are

considerably smaller in the FRAME condition than in the DARK condition for control subjects. These results are very similar to data reported before for young normal subjects (range between 20 and 40 years of age; see e.g. Soechting and Flanders, 1989a, 1989b; McIntyre et al., 1997, 1998; Admiraal et al., 2003). For the PD patient both the constant error and the variable error are considerably larger than for the control subject. The data for the PD patient, shown in Figure 6.2, reveal a clear overshoot of target position. The variable error for the PD patient was particularly enlarged in azimuth and elevation direction.

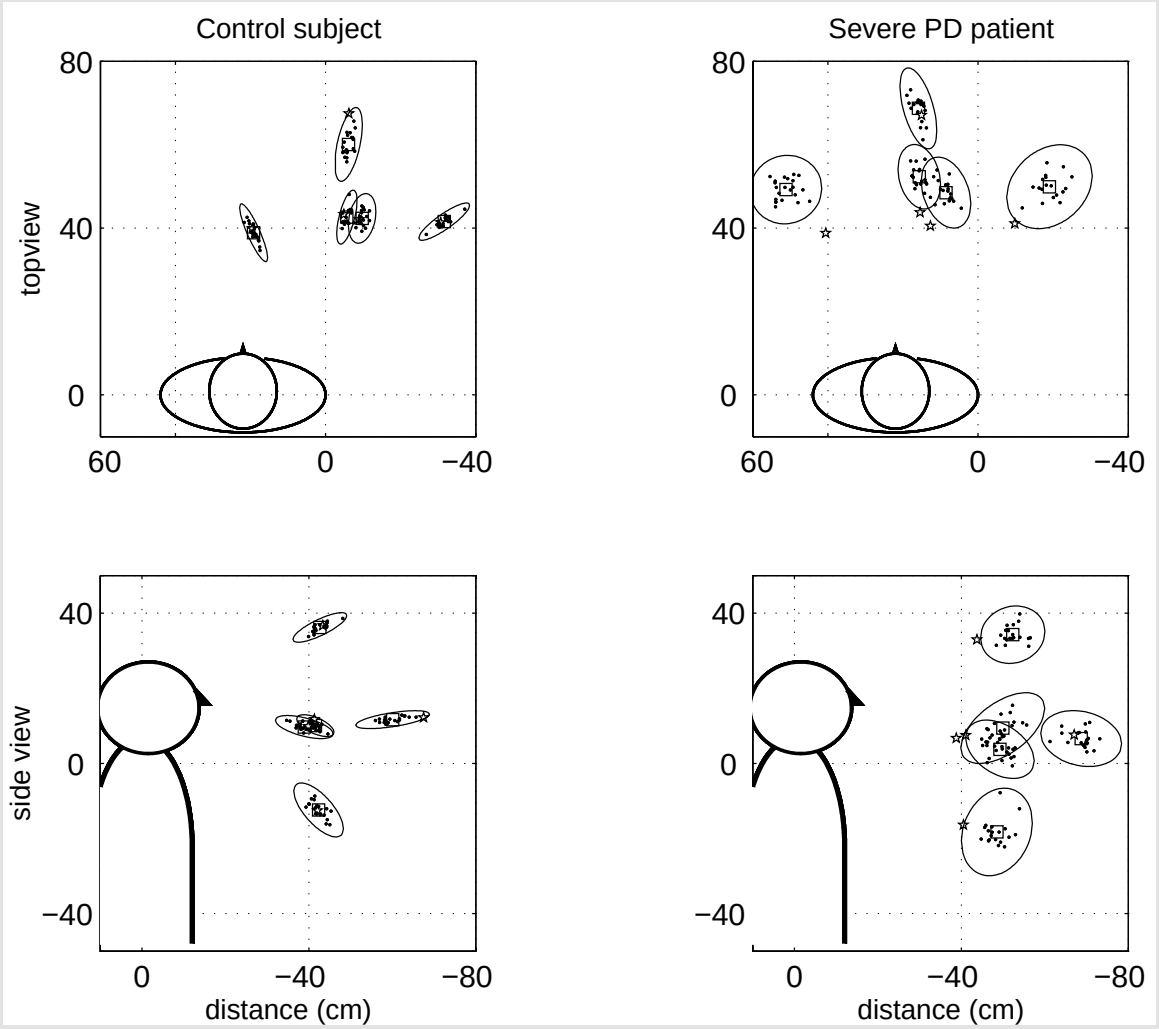

Figure 6.2. Top (upper panels) and side (lower panels) view of pointing positions (dots) to the 5 targets for a severe PD patient (left panels) and a control subject (right panels) in the FRAME condition. Stars indicate the actual position of the target, squares indicate the average pointing position and ellipses indicate the 95% confidence intervals. All targets and pointing positions are presented in an orthogonal coordinate system with the origin at the right shoulder of the subject.

Figure 6.3 illustrates the constant and variable errors for the groups of controls and patients in the DARK and FRAME conditions. Pointing errors were consistently smaller for

control subjects than for PD patients. This was apparent for both the constant errors (ANOVA, main effect of Group, $F_{1,19}$=6.6 , p<0.05) and the variable errors (ANOVA, main effect of Group, $F_{1,19}$= 5.9, p<0.05). Not surprisingly, the constant and variable errors were smaller in the FRAME condition than in the DARK condition (ANOVA, main effect of Condition, constant error: $F_{1,19}$ = 79.3, p<0.001; variable error: $F_{1,19}$ = 64.0, p<0.001). This effect was found both for the controls and the patients. Although the reduction of the errors in the FRAME condition relative to that in the DARK condition was somewhat larger for controls than for patients, the difference between controls and patients did not reach statistical significance, neither for the constant error (ANOVA, interaction effect of Group by Condition, $F_{1,19}$ = 0.98, p>0.3) nor for the variable error (ANOVA, interaction effect of Group by Condition, $F_{1,19}$ = 2.5, p>0.1). Because errors were somewhat larger for patients than for controls, we also calculated the relative decrease of the errors in the FRAME condition, relative to that in the DARK condition. This analysis showed that the relative reduction of the constant error was significantly smaller for patients (29.3 ± 13.1%) than for controls (45.0 ± 17.7%) (unpaired t-test, p<0.05). For the variable errors, the relative reduction did not differ significantly between patients (71.4 ± 21.7%) and controls (71.3 ± 30.5%) (unpaired t-test, p>0.95).

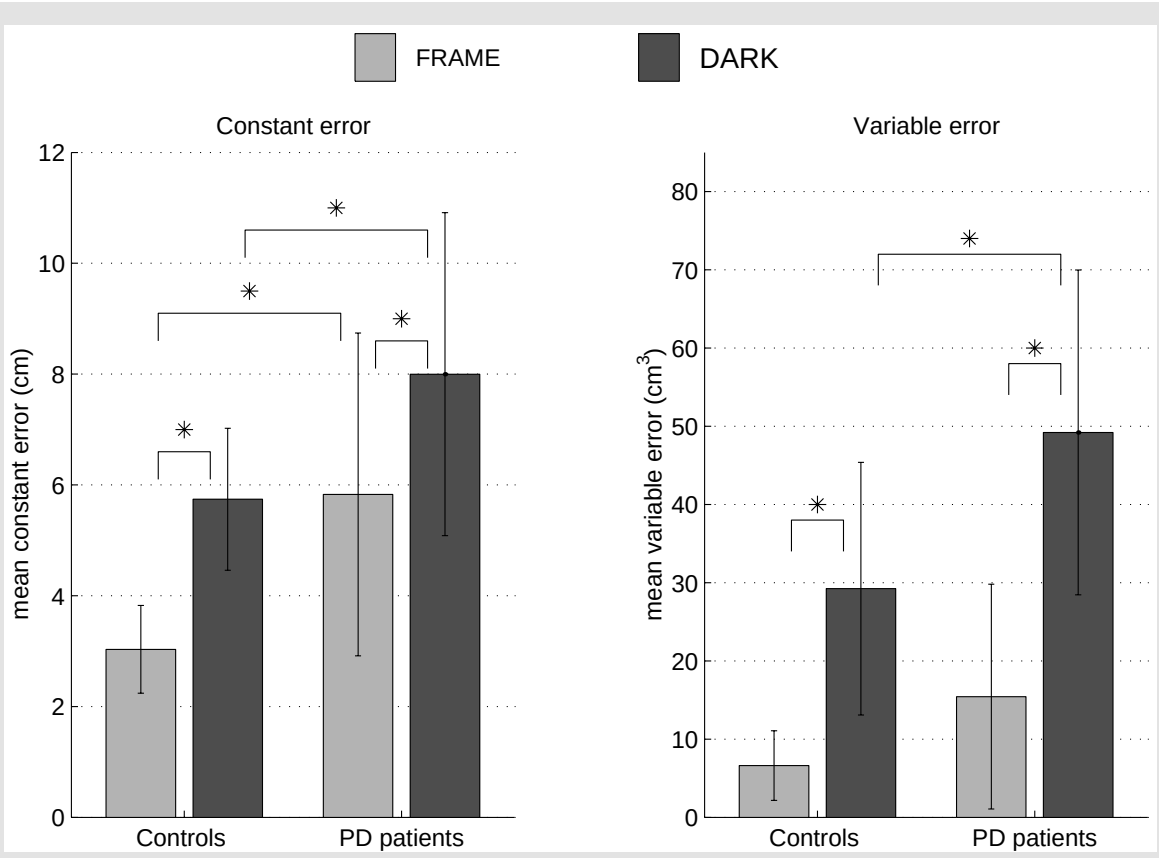

Figure 6.3. Mean constant (left panel) and variable error (right panel) for controls and PD patients. *= significant difference (P<0.05). Error bars represent the standard deviation.

Analysis of the spatial components of the constant error did not reveal a significant difference between the group of controls and the group of PD patients. However, the scatter of the constant errors was larger for the group of PD patients than for the group of controls in the FRAME condition in radial distance ($p<0.01$), azimuth ($p<0.05$), and elevation ($p<0.05$). The scatter was not significantly different for PD patients and controls in the DARK condition ($p>0.1$; $p>0.5$; $p>0.35$ for radial distance, azimuth and elevation, respectively). Both controls and PD patients showed the largest scatter in radial distance both in the DARK condition (approximately 1.8 times larger than for azimuth and elevation) and for the FRAME condition (approximately 2.8 times larger than azimuth and elevation).

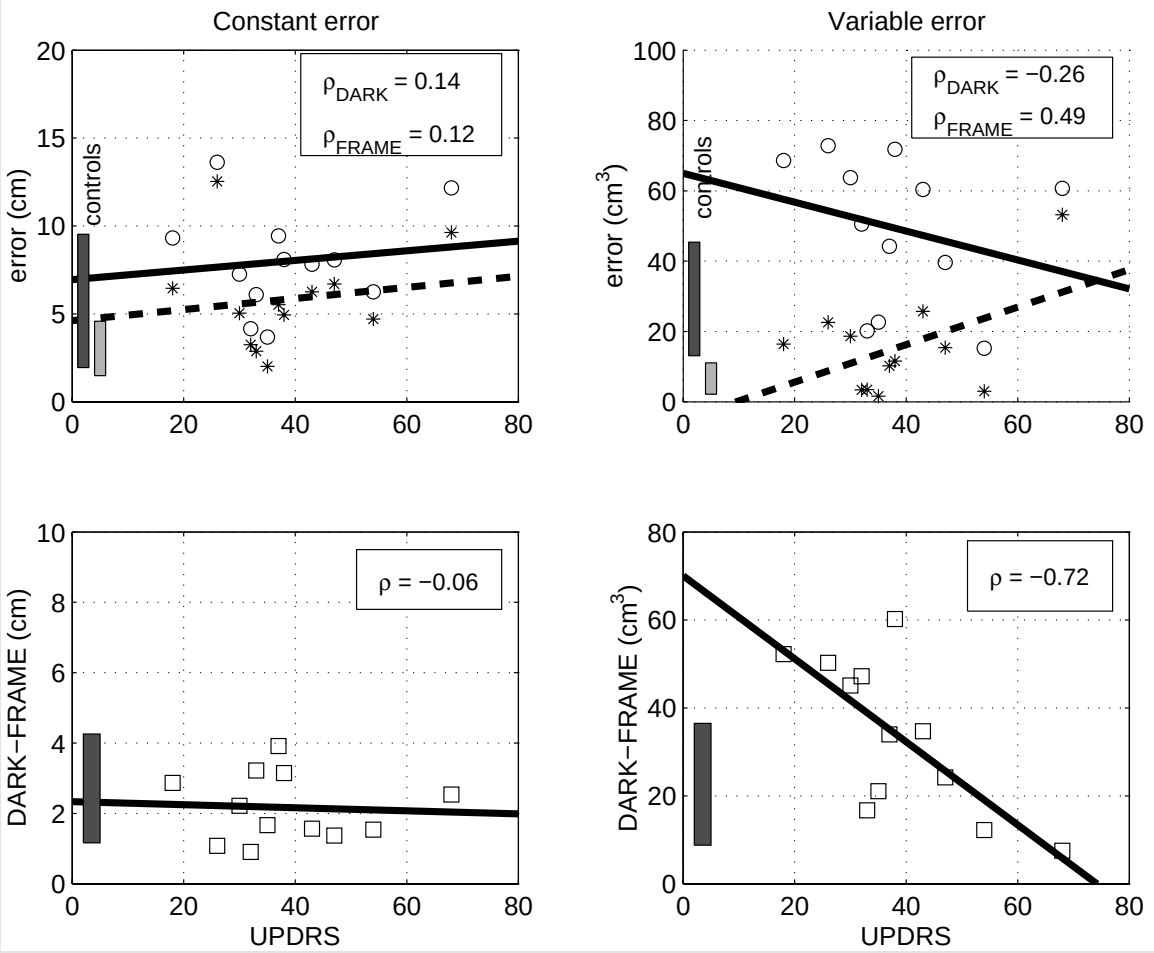

Figure 6.4. Relation between the UPDRS score (severity of the disease) and the constant error (left upper panel) and variable error (right upper panel). Errors are shown for the FRAME condition (stars, dashed line) and the DARK condition (circles, solid line). Lower panels show the difference of constant error (lower left panel) and variable error (lower right panel) in the DARK and FRAME condition (squares) for each patient as a function of the UPDRS score of that patient. Vertical bars on the left hand side of the panels represent the mean error plus or minus the standard deviation for control subjects in the DARK condition (black bars) and in the FRAME condition (gray bars).

Correlation analysis

The upper panels of Figure 6.4 show the constant error and the variable error (averaged over all targets) as a function of the severity of PD (UPDRS-score). The constant error (upper left panel in Figure 6.4) did not show a significant effect of the severity of PD in the DARK or in the FRAME condition. The average constant error is significantly smaller in the FRAME condition than in the DARK condition ($p<0.001$, paired t-test), but the slope as a function of the UPDRS-score was not significantly different ($p=0.96$) in the two conditions. Therefore, the difference of the constant error in the DARK and FRAME condition, which reflects the effect of visual information on the constant error, did not change with the UPDRS-score ($\rho=-0.06$; lower left panel in Figure 6.4).

For the variable error, there is a clear effect of the severity of PD. The variable error increases significantly with the UPDRS-score in the FRAME condition ($\rho=0.49$, $p<0.05$; upper right panel in Figure 6.4). The decrease of the variable error with the UPDRS-score in the DARK condition was not significant. The benefit of visual information for pointing to the remembered visual target becomes evident after subtraction of the error in the FRAME condition from that in the DARK condition. A large difference between the variable pointing errors in the DARK and FRAME condition points to a large benefit of visual information about finger position and the reference frame. The reduction of the variable error in the FRAME condition relative to that in the DARK condition showed a large and highly significant negative correlation ($\rho=-0.72$, $p<0.005$) with the severity of PD (lower right panel in Figure 6.4).

To obtain more insight in the orientation of the pointing errors relative to the subject, we calculated the spatial components of the variable error in spherical coordinates relative to the subject. The upper panels in Figure 6.5 show the components of the variable error in radial distance, azimuth and elevation as a function of the severity of PD. The variable error in radial distance, azimuth, and elevation did not show a significant correlation with the severity of PD in the DARK condition (see Figure 6.5). In the FRAME condition, the variable error did not show a significant correlation with the severity of PD for radial distance and azimuth direction. However, the variable error did show a significant positive correlation with the severity of PD for elevation ($\rho=0.52$, $p<0.05$).

The lower panels of Figure 6.5 show the difference between the variable errors in the DARK and FRAME condition for each of the spatial components. The differences for azimuth and elevation showed a significant negative correlation with the severity of PD ($\rho=-0.69$, $p<0.01$ and $\rho=-0.76$, $p<0.005$ for azimuth and elevation, respectively). The difference of the variable error in the FRAME and DARK condition did not show a significant relation with the severity of PD for the radial direction.

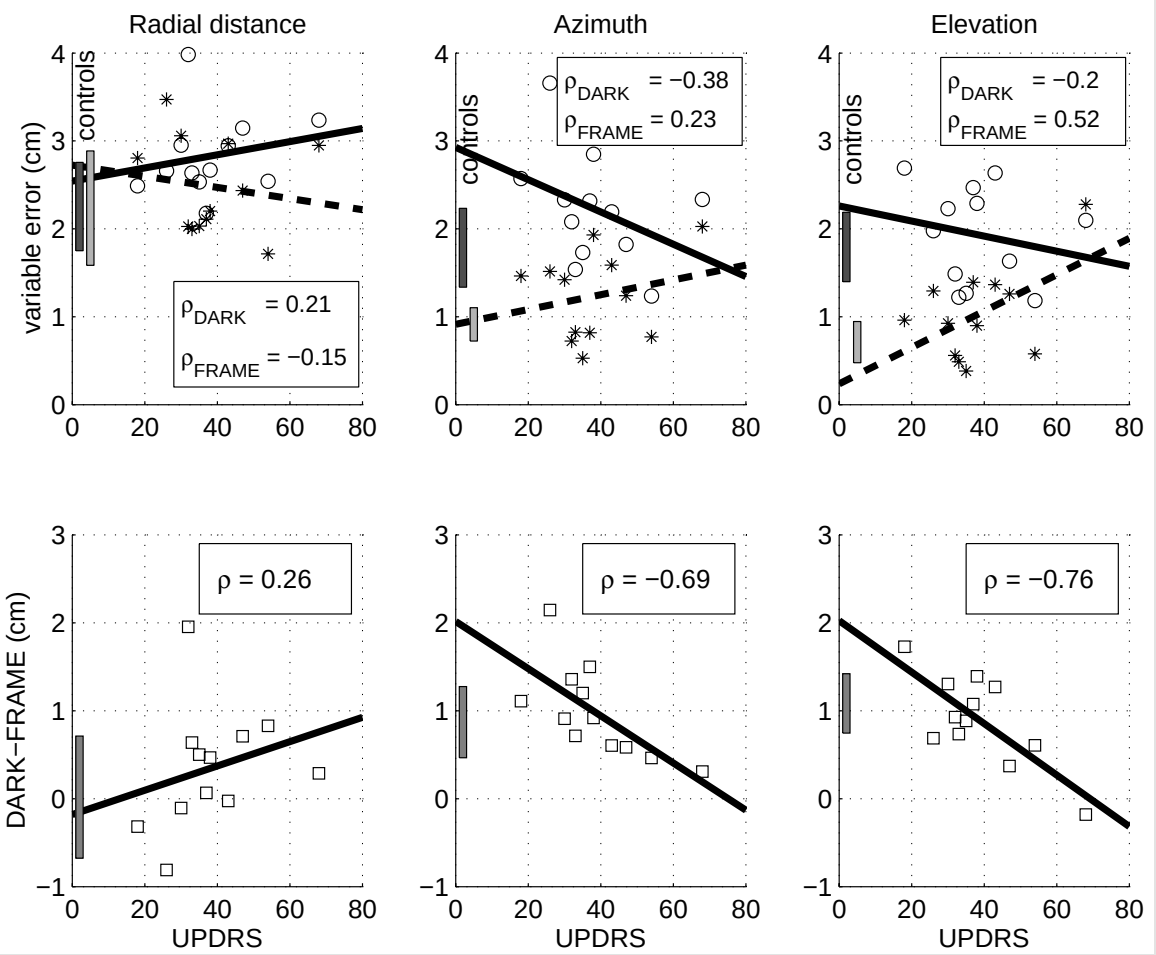

Figure 6.5. Upper panels show the spatial components of the variable error in radial distance (upper left panel), azimuth (upper middle panel) and elevation (upper right panel). Errors are shown for the FRAME condition (stars, dashed line) and the DARK condition (circles, solid line). Lower panels show the difference between the spatial components of the variable error in the DARK and FRAME condition. Vertical bars on the left hand side of the panels represent the mean error plus or minus the standard deviation for control subjects in the DARK condition (black bars) and in the FRAME condition (gray bars).

Discussion

In this study we investigated the effect of the severity of PD on the accuracy of pointing movements to remembered visual targets. On average, PD patients pointed less accurately than controls in the DARK and FRAME condition, which was evident from the larger constant errors in the FRAME and the DARK condition and from the larger variable error in the DARK condition compared to controls. The severity of PD hardly affected the constant error, but appeared to have a large effect on the variable error: the beneficial effect of visual feedback decreased markedly with increasing severity of PD.

Adamovich et al. (2001) studied pointing to remembered targets in PD patients in a

similar DARK condition and in a condition with a continuously lit LED on the finger but without visual information about the visual environment (so called “FINGER condition”). In agreement with our results, they reported that PD patients had larger variable errors and constant errors than controls in pointing to remembered targets in the DARK condition. In their FINGER condition they found larger variable errors for PD patients than for controls, but no significant difference between controls and patients was found for the constant error. In our FRAME condition, PD patients showed a significantly larger constant error than controls, but the variable errors were not significantly different. Therefore, we conclude that PD patients point less accurately than controls, especially in the absence of visual information, which is in agreement with results of previous studies on pointing movements in PD patients (Adamovich et al., 2001; Klockgether et al., 1994; Flash et al., 1992; Ketcham et al., 2003).

Subtracting the error in the FRAME condition from the error in the DARK condition reveals the effect of visual information in pointing movements. Control subjects showed a decrease in both the constant error and variable error in the FRAME condition, which was in agreement with previous observations on pointing to remembered visual targets (Soechting and Flanders, 1989a,b; McIntyre et al., 1997, 1998; Admiraal et al., 2003). PD patients showed a similar reduction in variable error and constant error between the FRAME and DARK condition. The main new finding of this study is a significant decrease of the *difference* of the variable error in the DARK and FRAME conditions as a function of the severity of PD (see lower right panel of Figure 6.4). This means that with increasing severity of PD, patients are less well able to use visual information to reduce the variability in their movements. This conclusion is supported by the specific effect of visual information on the spatial components of the variable error. The decrease of the variable error between the DARK and FRAME conditions was significantly correlated to the severity of PD for azimuth and elevation, but not for radial direction. This is exactly what one would expect if an effect of vision was involved since Van Beers et al. (2002) showed that vision mainly contributes to the accuracy in azimuth and elevation direction and less so in radial direction.

In principle, errors in pointing movements to remembered visual targets can be attributed to various factors, such as the misperception of the target position, errors in spatial memory, errors in the transformation from visual information to an appropriate motor command, or to a deficit in proprioceptive information processing of the arm. The obvious question then is: what is the underlying mechanism that is responsible for the larger error in PD patients? It has been hypothesized that spatial memory might be affected in PD patients. This hypothesis is not compatible with notion that mild to moderately affected PD patients make the same errors as controls when pointing to a remembered visual target with a Light-Emitting-Diode (LED) on their pointing fingertip in complete darkness (Adamovich et al., 2001) or when pointing to a remembered visual target with the eyes closed (Poizner et al., 1998). This is compatible with our finding that PD patients did not show significantly different

variable errors in the FRAME condition relative to control subjects (see right panel of Figure 6.3). Moreover, analysis of the spatial components of the constant error did not reveal differences between controls and PD patients in DARK and FRAME condition. These results argue against the hypothesis that misperception of target position or spatial memory might be responsible for the larger errors in PD patients. In addition, Ketcham et al. (2003) found an increase in the variability of end-point errors to remembered target locations in early PD patients. Since neither the delay, nor the number of items nor the sequence familiarity of the targets affected the end-point errors, this observation was interpreted as evidence in favor of the hypothesis that PD patients have an impairment in memory-motor transformation rather than an impairment in spatial memory. Other evidence against a possible role of spatial memory on pointing errors comes from Hodgson et al. (1999) who reported that PD patients and control subjects did not differ in the accuracy of eye movements to a single target (see also Crawford et al., 1989; Lueck et al., 1992). Therefore, we conclude that there is no evidence for misperception of target location or for an impairment in spatial memory to explain the larger pointing errors to remembered visual targets found in PD patients.

During the execution of a pointing movement, sensorimotor information can be used to correct for errors in end-point positions. In the absence of visual cues, subjects have to rely mainly on proprioceptive information to guide their index finger to the remembered visual target position (Soechting and Flanders, 1989a; 1989b; van Beers et al., 2002). Therefore, the observation of larger variable errors in the DARK condition for PD patients than for controls suggests that patients are less able to use proprioceptive information, in agreement with previous studies (Klockgether et al., 1995; Rickards and Cody, 1997; Jobst et al., 1997; Dimicri et al., 1997; Zia et al., 1999; Khudados et al., 1999; Lewis and Byblow, 2002). Neither the variable error nor the constant error showed a significant relation with the severity of PD in the DARK condition. This observation suggests that the deficit in the use of proprioceptive information occurs at an early stage of PD, and is hardly affected by furher disease progression. In early stages of the disease, the deficit in proprioceptive information processing is compensated by using visual feedback, because the variable error in the FRAME condition was the same for mildly affected PD patients and controls. However, with progression of the disease, the availability of visual information does not improve the variable error, indicating a deficit in visual information processing to guide pointing movements.

In conclusion, the main findings of this study are the following. Compared to controls, patients with PD made larger constant errors in pointing movements, both with and without visual feedback, which was independent of disease severity. Second, variable errors were larger in patients compared to controls, in particular for pointing movements without visual feedback. These variable pointing errors were influenced by disease severity, in such a way that the beneficial effect of visual feedback markedly decreased with more advanced disease severity. Taken together, these findings suggest that pointing movements in PD are impaired

because of a kinesthetic processing deficit, which appears early in the course of the disease, as well as by a visual feedback problem, which emerges in later stages of the disease.

Summary, Bibliography, and Publications

Summary

This thesis describes five studies to assess motor disorders in patients with Parkinson's disease. The first two chapters describe the development of an ambulatory device to assess levodopa induced dyskinesia. Movements of patients were measured using accelerometers placed at different body segments. Neural networks were trained using variables from the accelerometer signals and physicians rating to assess the severity of dyskinesia. The following chapter 4 used the trained neural networks to extract parameters, which are important to distinguish between dyskinesia and voluntary movements. Chapter 5 provides an example of using the method developed in chapter 3 for evaluating the effect of levodopa dose on the severity of dyskinesia. The final chapter investigates patients with Parkinson's disease and age-matched controls in pointing to remembered visual targets in complete darkness and in the presence of an illuminated visual reference frame. The next sections summarize the backgrounds, results, and conclusions of the studies described in this thesis

Chapter 2: Detection and Assessment of LID in a limited set of daily life tasks.

So far, Levodopa-induced dyskinesias (LID) in Parkinson's disease (PD) have remained a clinical challenge. In chapter two, we evaluated the feasibility of neural networks to detect LID and to quantify their severity using the data obtained by Hoff and coworkers (2001a). Sixteen PD patients were monitored at rest and during various activities of daily living. The movements of the patients were measured using 4 pairs of accelerometers mounted on the wrist, upper arm, trunk and leg on the most affected side. Using parameters obtained from the accelerometer signals, neural networks were trained to detect and to classify LID corresponding to the modified Abnormal Involuntary Movement Scale (m-AIMS). The Spearman rank correlation between the physicians rating and the neural network rating was considerably larger than that for the regression analysis for all daily life tasks. The regression analysis on the same data set in a previous study by Hoff et al. (2001a) failed in rating the severity of LID for body parts involved in voluntary movements. The neural networks were able to distinguish voluntary movements from LID and to assess the severity of LID. Important parameters for classification appeared to be the mean segment velocity and the cross-correlation between accelerometers on the arm, trunk and leg. Based on the results in this study, we conclude that neural networks are a valid and reliable method to detect and to assess the severity of LID corresponding to the m-AIMS scale.

Chapter 3: Automatic assessment of LID in daily life.

The results obtained in chapter two were far from optimal, indicating that considerable improvement is needed to obtain a reliable method that can be used to assess dyskinesia in

daily life. One of the reasons for this may be related to the limited set of tasks in which patients have been tested. The aim of the study in this chapter was to develop an objective and automatic procedure to assess the severity of levodopa induced dyskinesia (LID) in patients with Parkinson's disease during daily life activities. Thirteen patients were continuously monitored in a home-like situation for a period of approximately 2.5 hours. During this 2.5-hour period, the patients performed about 35 functional daily-life activities. Behavior of the patients was measured using triaxial accelerometers, which were placed at 6 different positions of the body. A neural network was trained to assess the severity of LID using various variables of the accelerometer signals. Neural network scores were compared with the assessment by physicians, who evaluated the continuously videotaped behavior of the patients off-line. The neural network correctly classified the severity of dyskinesia in 1-minute intervals in 83.0, 77.0, and 76.9 for the trunk, arm and leg, respectively. In the few cases of misclassification, the rating by the neural network was in the class next to that indicated by the physicians using the AIMS-score (scale 0 to 4). From a clinical point of view, physicians are mainly interested in whether patients suffer from dyskinesia for at least a few minutes. For periods of 15 minutes, the neural network correctly classified dyskinesia or the absence of dyskinesia in 93.7, 99.7 and 97.0% for the arm, trunk and leg, respectively. The results indicate that the neural network can accurately assess the severity of LID and could distinguish LID from voluntary movements in daily life situations.

Chapter 4: Important parameters in the assessment of dyskinesia.

In chapter 3, we have demonstrated that neural networks are highly successful to detect dyskinesia and to distinguish dyskinesia from voluntary movements. The aim of the study in chapter 4 was to use the trained neural networks to extract parameters, which are important to distinguish between dyskinesia and voluntary movements. Analysis of the neural networks revealed several new variables, which are relevant for assessing the severity of LID. For the trunk and the leg, the important parameters appeared to be the percentage of time that the trunk or leg was moving and the standard deviation of the segment velocity of the less dyskinetic leg. For the arm the combination of the percentage of time, that the wrist was moving, and the percentage of time, that a patient was sitting, explained the largest part of the variance of the output. In addition, dyskinesia differs from voluntary movements in the fact that dyskinetic movements tend to have lower frequencies than voluntary movements and in the fact that movements of different body segments are not well coordinated in dyskinesia.

Chapter 5: Effect of levodopa dose on dyskinesia in advanced PD.

After several years of levodopa medication, many patients with Parkinson's disease (PD) have non-existent or small therapeutic windows. In this study, the effect of levodopa

dose on the severity of dyskinesia was evaluated during mental and motor daily life activities in patients with advanced Parkinson's disease. Patients took double blind 1, 1½, and 2 times the usual effective levodopa dose at three different visits. During each visit they performed several daily life activities. The severity of dyskinesia was assessed using the method described in chapter 3. On average, patients showed the smallest severity of dyskinesia for the usual levodopa dose (1 dose). The severity of dyskinesia was larger for the 1½ and 2 usual levodopa doses compared to the usual dose whereas the severity of dyskinesia did not differ between the 1½ and 2 usual levodopa doses. Across patients there were large inter-individual differences in responses to different levodopa doses.

Chapter 6: Differential progression of proprioceptive and visual information processing deficits in Parkinson's disease.

Recent studies have suggested that patients with Parkinson's disease (PD) have deficits in processing of sensory inputs, particularly proprioceptive feedback. The accuracy of pointing movements depends to a large extent on the availability of visual and proprioceptive information. Animal studies have shown that the ability to use visual and proprioceptive information depends on the degree of dopamine deficits in the substantia nigra, suggesting that deficits in sensory information processing in PD may be related to the disease severity. In this study we tested pointing movements to remembered visual targets in PD patients with a range of disease severities and age-matched controls. Both groups were tested under two conditions: pointing to a remembered visual target in complete darkness (DARK) and in the presence of an illuminated cubic frame with a light attached to the tip of the index finger (FRAME). In the DARK condition, proprioceptive information is the most reliable source of information whereas in the FRAME condition, subjects can rely on visual information. We analyzed constant errors as a measure of the general error in planning and execution of the pointing movement and variable errors as a measure of the noise in planning and execution. PD patients showed larger constant errors than controls in the DARK and FRAME condition. The constant error was not related to disease severity (UPDRS motor score) in the DARK or FRAME conditions. The variable error was larger in PD patients compared to controls, in particular for pointing movements in the DARK condition. The variable error increased significantly with disease severity in the FRAME condition, but not in the DARK condition. In addition, the benefit of visual information (evaluated by subtracting the variable error in the FRAME condition from that in the DARK condition) decreased markedly with disease severity. These results suggest that pointing movements in PD are impaired because of a kinesthetic processing deficit, which appears early in the course of the disease, as well as a visual feedback problem, which emerges in later stages of the disease.

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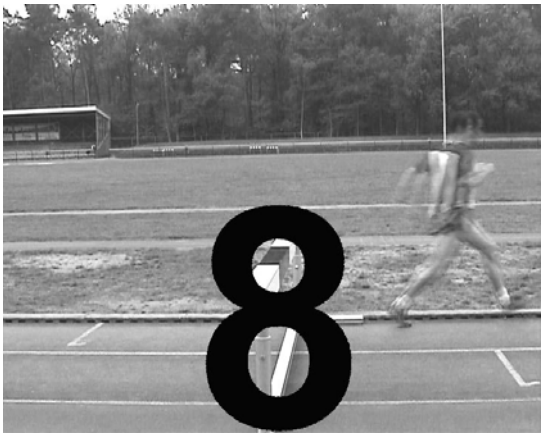
Samenvatting, Dankwoord en Curriculum Vitae



Samenvatting

De ziekte van Parkinson wordt gekenmerkt door verschillende symptomen zoals tremor (beven), bradykinesie (langzaam bewegen), hypokinesie (weinig bewegen) en rigiditeit (stijfheid). De ziekte van Parkinson wordt veroorzaakt door een tekort aan dopamine productie in de Substantia Nigra, een klein gebiedje in de hersenen. Een medicijn voor het genezen van de ziekte van Parkinson is nog steeds niet voor handen. In het begin stadium van de ziekte verdwijnen de symptomen van de ziekte van Parkinson echter na inname van levodopa. In de eerste jaren van de ziekte kan nog worden volstaan met lage doseringen levodopa, maar na enkele jaren zijn hogere doseringen noodzakelijk om de Parkinson symptomen te onderdrukken. Als gevolg van de ziekte en langdurige levodopa medicatie treden er bijverschijnselen op. Deze bijverschijnselen zijn onder andere niet vrijwillige, overtollige bewegingen (dyskinesie) en blijken in grote mate afhankelijk te zijn van de ingenomen levodopa dosering. Omdat deze dyskinesie het gevolg is van levodopa wordt deze ook wel levodopa geïnduceerde dyskinesie genoemd. In deze samenvatting zullen we dit kortweg aanduiden met dyskinesie. Het behandelen van Parkinson patiënten met dyskinesie wordt steeds moeilijker. Immers, de levodopa medicatie moet voldoende zijn om de Parkinson symptomen te laten verdwijnen, maar mag ook niet te veel zijn omdat anders de patiënten hinder ondervinden van dyskinesie. De levodopa medicatie moet voor deze patiënten dus zo optimaal mogelijk worden ingesteld om de minste hinder van de ziekte van Parkinson te ondervinden.

Voor de juiste levodopa medicatie dient men te weten op welke tijdstippen een patiënt goed functioneert, last heeft van Parkinson symptomen of juist last heeft van dyskinesie. Om dit te achterhalen moet de patiënt zijn functioneren zelf bijhouden in de vorm van een dagboek. Deze manier van bijhouden is echter arbeidsintensief en daarbij zijn patiënten vaak erg subjectief (niet betrouwbaar) in het beoordelen van hun eigen functioneren. Een automatisch systeem dat objectief het functioneren van een Parkinson patiënt registreert zou dus een uitkomst zijn. De moeilijkheid van zo'n automatische registratie schuilt in het feit dat je in staat moet zijn om vrijwillige bewegingen te onderscheiden van dyskinesie. Een van de belangrijkste doelstellingen van dit proefschrift is een methode te ontwikkelen om dyskinesie automatisch te registreren en te classificeren op een objectieve manier.

Dit proefschrift beschrijft vijf studies gericht op het detecteren van motorische problemen bij patiënten met de ziekte van Parkinson. De eerste twee hoofdstukken beschrijven de ontwikkeling van een ambulant apparaat voor het meten van levodopa geïnduceerde dyskinesie. Bewegingen van patiënten werden gemeten met accelerometers bevestigd op verschillende segmenten van het lichaam. Neurale netwerken werden "getraind" om de ernst van dyskinesie te bepalen, met parameters berekend uit de

accelerometer signalen als input en scores van de arts als output. In hoofdstuk 4 zijn de parameters bekeken die belangrijk zijn in het onderscheiden van dyskinesie en vrijwillige bewegingen. Hoofdstuk 5 geeft een voorbeeld van het gebruik van de ontwikkelde methode in hoofdstuk 3 voor het evalueren van het effect van levodopa medicatie op de ernst van de dyskinesie bij patiënten met gevorderde Parkinson. In het laatste hoofdstuk worden patiënten met de ziekte van Parkinson en leeftijd gebonden controle personen gemeten tijdens het reproduceren van de positie van een herinnerd visueel doel in complete duisternis en in de aanwezigheid van een visueel referentie kader. De volgende paragrafen geven een korte samenvatting van de achtergronden, resultaten en conclusies van de studies in dit proefschrift.

Hoofdstuk 2: Detectie en bepaling van dyskinesie in een beperkt aantal taken uit het dagelijks leven.

Tot dusver is dyskinesie bij patiënten met de ziekte van Parkinson moeilijk te behandelen. In hoofdstuk 2, worden de mogelijkheden van neurale netwerken geëvalueerd voor het detecteren en kwalificeren van de ernst van de dyskinesie, gebruik makend van de gegevens verkregen door Hoff en collega's. Zestien Parkinson patiënten werden geobserveerd tijdens rust en gedurende een aantal taken uit het dagelijks leven zoals drinken, jas aandoen en wandelen. De bewegingen van de patiënten werden geregistreerd met 4 paar accelerometers bevestigd op de pols, de bovenarm en het bovenbeen aan de meest aangedane zijde en op de romp. Neurale netwerken werden gebruikt om dyskinesie te detecteren en de ernst van dyskinesie te classificeren met de AIMS-schaal. De AIMS-schaal geeft een waarde tussen 0 en 4 en wordt door een arts gegeven aan een patiënt na observatie (0 wil zeggen geen dyskinesie en 4 wil zeggen zeer ernstige dyskinesie). De Spearman rank correlatie tussen de score van de arts en de score van het neuraal netwerk was groter dan de Spearman rank correlatie verkregen met de regressie analyse verkregen in het onderzoek door Hoff en collega's. Daarnaast, bleek de regressie analyse geen goede score te geven voor lichaamssegmenten die betrokken waren bij vrijwillige bewegingen, zoals de arm tijdens drinken. Het neurale netwerk bleek wel in staat te zijn om onderscheid te maken tussen vrijwillige bewegingen en dyskinesie. Belangrijke parameters, die het neurale netwerk gebruikte, waren de gemiddelde snelheid van een lichaamssegment en de kruiscorrelatie tussen de arm, romp en been. Op basis van de resultaten in deze studie werd geconcludeerd dat het gebruik van neurale netwerken een valide en betrouwbare methode is voor het detecteren en bepalen van de ernst van dyskinesie op de AIMS-schaal.

Hoofdstuk 3: Het automatische detecteren van dyskinesie in het dagelijks leven

De resultaten verkregen in hoofdstuk 2 waren niet helemaal optimaal. Dit betekende dat een verbetering nodig was om de methode betrouwbaar en toepasbaar te maken in het

dagelijks leven. Een reden voor de niet optimale prestatie was het beperkte aantal taken waarin bewegingen van patiënten werden geregistreerd. Het doel van hoofdstuk 3 was om een objectieve en automatische methode te ontwikkelen die dyskinesie kan bepalen in het dagelijks leven. Dertien patiënten werden continu geregistreerd in een huiselijke omgeving tijdens een periode van ongeveer 2,5 uur. Gedurende deze 2,5 uur werden ongeveer 35 verschillende taken uit het dagelijks leven uitgevoerd. De bewegingen van de patiënten werd geregistreerd met tri-axiale accelerometers bevestigd op 6 verschillende lichaamssegmenten (beide bovenarmen en bovenbenen, de romp en op de pols van de meest aangedane zijde). Een neuraal netwerk werd getraind met de verschillende parameters, die berekend werden uit de signalen van de accelerometers als input en de mate van dyskinesie op de AIMS-schaal gegeven door een arts als output. Vervolgens werd het getrainde netwerk getest met parameters van de signalen van de accelerometers en de daarbij behorende mate van dyskinesie gegeven door de arts, die niet waren gebruikt gedurende de training van het neurale netwerk. Het neuraal netwerk classificeerde de ernst van de dyskinesie gelijk aan de ernst gegeven door een arts in 83,0, 77,0 en 76,9% voor tijdsintervallen van 1 minuut voor respectievelijk de romp, arm en been. In het geval dat het neuraal netwerk de ernst van de dyskinesie fout classificeerde gaf het netwerk hooguit een verschil van 1 schaal met de waarde gegeven door de arts. Voor periodes van 15 minuten gaf het netwerk in 93,7, 99,7 en 97,0% van de tijd correct aan of er sprake was van dyskinesie of afwezigheid van dyskinesie. De resultaten gaven aan dat het neurale netwerk nauwkeurig kan bepalen wat de ernst van de dyskinesie is en dat het onderscheid kan maken tussen dyskinesie en vrijwillige bewegingen.

Hoofdstuk 4: Parameters die dyskinesie onderscheiden van vrijwillige bewegingen.

In hoofdstuk 3 hebben we laten zien dat het neurale netwerk zeer succesvol is in het detecteren van dyskinesie en goed onderscheid kan maken tussen dyskinesie en vrijwillige bewegingen. De doelstelling van hoofdstuk 4 was om te definiëren welke parameters het neurale netwerk gebruikt om een onderscheid te maken tussen dyskinesie en vrijwillige bewegingen. Analyse van het neuraal netwerk gaf nieuwe variabelen, die van belang zijn bij het bepalen of iemand dyskinetisch is of juist vrijwillige bewegingen maakt. Voor de romp en de benen was het percentage van de tijd dat de romp of benen bewogen en de standaard deviatie van de snelheid van het meest aangedane been de belangrijkste parameters. De belangrijkste parameters voor de arm waren het percentage van de tijd dat de pols bewoog en het percentage van de tijd dat een patiënt zat. Dyskinesie verschilt van vrijwillige bewegingen door dat dyskinetische bewegingen lagere frequenties hebben dan vrijwillige bewegingen en door dat bewegingen van verschillende lichaamssegmenten minder goed met elkaar geccorreleerd zijn tijdens dyskinesie

Hoofdstuk 5: Effect van levodopa op dyskinesie bij patiënten met gevorderde Parkinson

Na een aantal jaren van levodopa medicatie hebben veel patiënten met de ziekte van Parkinson een kleine of zelfs geen therapeutisch window meer. Dit betekent dat ze of last hebben van Parkinson symptomen of dyskinetisch zijn en er geen overgangsgebied meer is waarin geen hinder wordt ondervonden van de gevolgen van de ziekte. Het doel van dit onderzoek was om het effect van de levodopa dosis op de ernst van de dyskinesie te evalueren gedurende mentale en motorische taken uit het dagelijks leven bij Patiënten met gevorderde Parkinson. Patiënten namen dubbel blind 1, 1½ en 2 keer de normale effectieve levodopa dosering tijdens drie verschillende bezoeken. Gedurende elk bezoek werden verschillende taken uit het dagelijks leven uitgevoerd. De mate van dyskinesie werd bepaald met behulp van de methode ontwikkeld in hoofdstuk 3. Gemiddeld lieten patiënten de minste dyskinesie zien bij de normale effectieve levodopa dosering (1 dosis). De mate van dyskinesie was hoger voor de 1½ en 2 levodopa dosering vergeleken met de normale levodopa dosering. De 1½ en 2 keer de dosering verschilden niet met elkaar in de mate van dyskinesie. Echter, patiënten lieten individueel veel verschillende reacties zien op de levodopa dosering.

Hoofdstuk 6: Het effect van de ziekte van Parkinson op het reproduceren van de positie van een visueel herinnerd doel.

Uit recent onderzoek blijkt dat patiënten met de ziekte van Parkinson problemen hebben met het verwerken van sensorische informatie en in het bijzonder met de verwerking van proprioceptieve informatie. De nauwkeurigheid waarmee de positie van een visueel herinnerd doel kan worden gereproduceerd met de vinger blijkt in grote mate afhankelijk te zijn van de visuele informatie en andere sensorische informatie die gebruikt kan worden. Dierexperimenteel onderzoek heeft aangetoond dat de mogelijkheid om gebruik te maken van visuele en sensorische informatie afhangt van de mate van dopamine productie in de Substantia Nigra. Dit suggereert dat het probleem in verwerken van sensorische informatie afhankelijk zou kunnen zijn van de ernst van de ziekte. In dit onderzoek werden patiënten met de ziekte van Parkinson en controle personen getest terwijl zij de positie van visueel herinnerde doelen moesten reproduceren met de wijsvinger. Beide groepen werden in 2 condities getest: in een volledig donkere kamer (DARK) en in de aanwezigheid van een lichtgevend referentie kader om de herinnerde doelen heen en een lichtje op de wijsvinger (FRAME). In de DARK conditie is proprioceptieve informatie de meest betrouwbare informatie terwijl in de FRAME conditie, proefpersonen vermoedelijk juist visuele informatie gebruiken. De constante fout is de afstand tussen de gemiddelde aangewezen positie en de werkelijke positie van het visuele doel en geeft de algemene fout in het uitvoeren van de taak aan. De variabele fout representeert de variatie van de positie rond de gemiddelde

aanwijspositie en geeft de ruis in het uitvoeren van de taak aan. Patiënten met de ziekte van Parkinson maakten grotere constante en variabele fouten in de DARK en FRAME conditie vergeleken met de fout in het aanwijzen van de controle personen. De grootte van de constante fout bleek niet gerelateerd te zijn aan de ernst van de ziekte. De variabele fout bleek echter toe te nemen met de ernst van de ziekte in de FRAME conditie maar niet in de DARK conditie. Bovendien bleek het voordeel dat patiënten hadden door de beschikbare visuele informatie in de FRAME conditie (verschil tussen DARK en FRAME) af te nemen naarmate patiënten ernstigere symptomen van de ziekte van Parkinson hadden. De resultaten van dit onderzoek suggereren dat het reproduceren van de positie van herinnerde doelen is aangedaan bij patiënten met de ziekte van Parkinson door een probleem met de verwerking van proprioceptieve informatie, hetgeen zich in een vroeg stadium van de ziekte openbaart. Daarnaast is er ook een probleem met het gebruik maken van visuele informatie, maar dat openbaart zich pas geleidelijk in een later stadium van de ziekte.

Dankwoord

De bel voor de laatste ronde klonk als muziek in mijn oren. Mijn benen voelden als lood maar de eindsprint kon ik inzetten. Vijf obstakels moesten er nog worden genomen. De eerste balk ging eenvoudig en werd snel genomen. Het vervolg leek even mis te gaan maar na een korte aarzeling zette ik toch weer aan voor balk twee en drie. Een persoonlijk record moest erin zitten. De altijd lastige waterbak was het volgende obstakel. Voordat ik het wist stond mijn linker voet al in het water en begon ik aan de werkelijke eindsprint. De laatste balk ging in volle vaart en nu kon er eigenlijk niets meer mis gaan. In de laatste meters schoten de mensen, die mede verantwoordelijk waren voor het halen van de finish, door mijn hoofd.

Voor de eerste trainingen heb ik gebruik kunnen maken van de faciliteiten geboden door de Leidse groep. Zonder de medewerking van Jorrit Hoff en Bob van Hilten zou ik deze wedstrijd nooit begonnen zijn. Hoofdcoaches Stan en Martin waren van het begin meteen van veel waarde en bleven dit ook gedurende al die jaren. Stan met zijn technische en wetenschappelijke begeleiding en Martin met zijn enorme praktijkervaring. Beide waren tijdens elke training en wedstrijd wel aanspreekbaar.

Al die jaren van training had ik zeker niet kunnen volbrengen zonder mijn trainingsmaatjes van de atletiek vereniging A.V. Medische Fysica & Biofysica. In het begin liepen Taylan en Niels aan mijn zijde en vrolijkten zij de trainingen op met Jazz muziek vergezeld door Ca^{+}-oscillaties van Niels en “ping-pings” van Taylan. De jaren erna werd Marjan mijn vaste trainingspartner. We werden elkaars mental coaches om elkaar door de zware trainingen heen te loodsen. Ik laat je dan ook met plezier iets eerder de finishlijn passeren.

Daarnaast waren er nog vele leden van A.V. Medische Fysica & Biofysica die het tot een plezierige vereniging maken. Ieke, Henk en Joyce en vele andere collega’s waren altijd wel te vinden voor een praatje tijdens of na het werk. Rens en Ronald bedank ik speciaal voor het laten winnen met darten. Eveneens mogen de theezetters niet worden vergeten die altijd weer voor goede hersteldrankjes zorgden. Chris, “het laatste biertje” na een zware training smaakte ook altijd goed. Pieter, Hans en Ger bedank ik voor de heerlijke hersteltraining tijdens de pauze op woensdagmiddag.

De technische ondersteuning van Hans, Ton, Co, Ger en Gunther zorgde er altijd voor dat het materiaal in orde was voor elke training en wedstrijd. Margiet, Judith en Annet wil ik graag bedanken voor het doorgeven van de rondetijden en het altijd luisterend oor. Wietske, Ingrid en Linda wil ik danken voor de hulp die zij mij boden tijdens de trainingen.

De trainingstage in Chicago werd een groot succes dankzij de enorme gastvrijheid van de Familie Verhagen. Ik blijf met plezier terugdenken aan deze Nederamerikaanse familie, waarvan ik me gedurende mijn verblijf toch een beetje een onderdeel voelde. Bas en Lex hebben me met waardevol advies bijgestaan op de techniektrainingen voor de

waterbakpassage met hoofdstuk 6 als mooi resultaat.

Natuurlijk waren er ook nog altijd de sponsors die het mogelijk maakten dat ik na elke training weer sneller kon herstellen door de vitaminepillen. Zo was daar de hoofdsponsor Het Prinses Beatrix Fonds, maar ook de subsponsor De Parkinson Patienten Vereniging mag niet vergeten worden. Deze wedstrijd had niet gelopen kunnen worden zonder de vrijwillige inzet van de Parkinson patiënten.

Op dat moment hoefde ik nog maar één stap te zetten om de finish te passeren en zag ik Miranda mij met haar grote glimlach opwachten en mijn ouders in de verte juichen. De steun van mijn ouders en familie is altijd een vaste waarde en een bron van rust geweest. Zonder Miranda, mijn trouwste coach, supporter en trainingsmaatje zou ik minder plezier in mijn leven hebben.

Curriculum vitae

Noël Keijsers werd op 22 mei 1973 geboren te Budel. De lagere schooltijd bracht hij door op de St. Anna school in Budel. In 1992 behaalde hij het VWO diploma aan het Bisschoppelijk College te Weert, waarna hij startte met de opleiding Bewegings-wetenschappen aan de Vrije Universiteit te Amsterdam. Tijdens zijn verschillende stages kreeg hij steeds meer lol in het doen van onderzoek. Na zijn afstuderen en een fietsreis door Peru begon hij dan ook als junioronderzoeker op de afdeling Medische Fysica en Biofysica aan de Katholieke Universiteit Nijmegen. Het doel van het project was om overbeweeglijkheid in het dagelijks leven automatisch te classificeren bij patiënten met de ziekte van Parkinson. Na succesvolle resultaten in het eerste jaar werd het project omgezet in een promotieonderzoek. De resultaten van dit onderzoek staan in dit proefschrift geschreven. Vanaf mei 2003 heeft hij een subsidie gekregen om dit onderzoek een goed vervolg te geven. In het vervolgonderzoek zal gepoogd worden om naast het classificeren van overbeweeglijkheid eveneens automatisch te bepalen of iemand last heeft van symptomen van de ziekte van Parkinson (automatisch classificeren van de “off-perioden”). Naast het werk is zijn grote passie hardlopen en in het bijzonder steeple. Om van deze activiteiten uit te rusten gaat hij het liefst per fiets of te voet de bergen in.